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PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING

FDA Briefing Document

October 21, 2014

NDA# 203188: ivacaftor oral tablets (trade name Kalydeco) for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene.

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the new drug application (NDA) 203188, ivacaftor oral tablets, for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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DIVISION MEMORANDUM

Date: September 23, 2014

From: Anthony G. Durmowicz, MD
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To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for supplemental New Drug Application (sNDA # 203188), for ivacaftor tablets (trade name Kalydeco) for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene.

I. Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on October 21, 2014. As members of the PADAC you provide important expert scientific advice and recommendation to the US Food and Drug Administration (the Agency) on various regulatory decisions. The upcoming meeting is to discuss the NDA from Vertex Pharmaceuticals for ivacaftor tablets (trade name Kalydeco) for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene.

Ivacaftor is a small molecule drug that has been shown to increase chloride ion transport across the CFTR chloride channel (the ion channel which, if defective results CF) in epithelial cell membranes and, as such, is classified as a "CFTR potentiator". The initial ivacaftor clinical program was previously conducted in a subpopulation of CF patients felt most likely to be responsive to CFTR potentiation by ivacaftor; a subpopulation defined by a having a mutation in the *CFTR* gene (*G551D*) that results in faulty ion channel regulation, commonly referred to as a "gating" defect. Vertex subsequently submitted the original NDA for ivacaftor oral tablets on October 18, 2011, and ivacaftor was approved for use in patients aged 6 years and older with a *G551D* mutation on January 31, 2012. Based partially on those results, Vertex applied for and received FDA Breakthrough Therapy designation on November 13, 2012, for the treatment of CF in patients with *CFTR* gene mutations that result in CFTR ion channel "gating" defects (those resulting in functional *CFTR* defects similar to the *G551D* mutation) and/or a different kind of mutation in the *CFTR* that results in residual baseline CFTR channel function of which the *R117H* mutation belongs. Development under that program resulted in ivacaftor being approved to treat CF in a subpopulation of patients defined by having at least one of 8 additional "gating" mutations in the *CFTR* gene on February 21, 2014. The discussion of efficacy data submitted by Vertex to support approval of ivacaftor for treatment of the subpopulation of CF patients defined by having a *R117H* mutation in the *CFTR* gene will be the main topic at the October 21, 2014, PADAC meeting.

This memorandum summarizes the contents of the Agency background material and the key issues and topics for discussion at the meeting. While the discussion will include safety, the focus of the meeting will be on efficacy and whether the submitted data support the efficacy of Kalydeco for the proposed indication (CF patients 6 years of age and older with a *R117H* mutation in the *CFTR* gene). The briefing package includes the following: clinical briefing document, statistical briefing document, and the current prescribing information for Kalydeco. The materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Vertex. These background materials represent preliminary findings, and do not represent the final position of the Agency. An important piece in our decision on this application will be the opinions and input that we receive from you at this meeting.

II. Background

Cystic Fibrosis (CF) Background

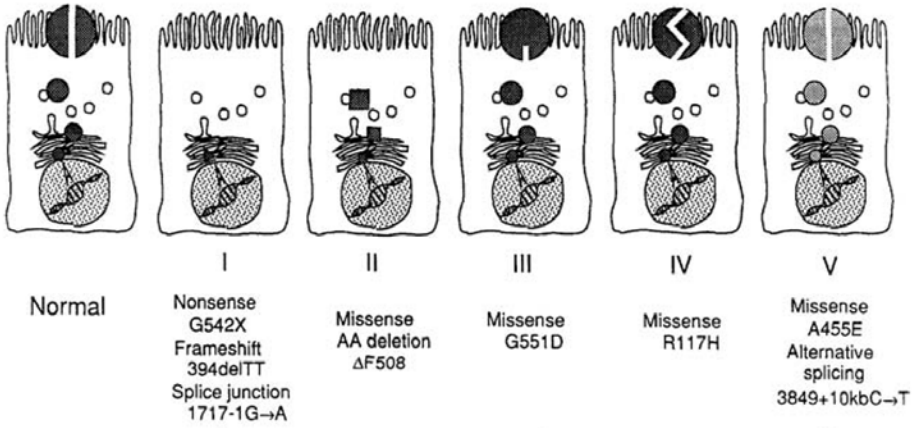
CF is a life-threatening autosomal recessive disease which affects about 70, 000 individuals world-wide (30,000 in US). It is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene that results in lack of or inadequate function of the CFTR protein on the surface of epithelial cells. The CFTR protein is a chloride channel that helps regulate salt and water absorption and secretion across epithelial cells. There are about 2000 mutations that have been identified in the *CFTR*; as an autosomal recessive disease, patients need mutations in both *CFTR* alleles to develop CF. General types of *CFTR* mutations have been classified based on the functional effect of the mutation on the CFTR protein (see Figure 1 below). Clinical manifestations of CF are dependent on types of mutations, post-transcriptional modification of CFTR protein, and environmental factors. Typically, the lungs, GI system (intestines, pancreas, liver), and reproductive systems are the predominantly affected organs systems. Death is usually due to respiratory failure as a result of obstructive lung disease and chronic pulmonary infection. Ultimately, disease severity depends on the type of mutations present and well as other modifying factors, however, currently the mean age of death is the mid- to late 30's.

Ivacaftor

Ivacaftor is a small molecule drug identified by high-throughput screening that has been shown to increase chloride ion transport across the CFTR chloride channel in epithelial cell membranes and, as such, is classified as a "CFTR potentiator". It is currently approved in the USA for the treatment of patients with CF defined by having one of nine functionally related mutations in the *CFTR (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R).* These mutations have in common the fact that they all fall into a category of mutation called "gating mutations" (type III in the Figure below) that reflect the CF population initially predicted to best benefit from ivacaftor, i.e., those patients with mutations where the resultant abnormal CFTR ion channel has faulty ion regulation but can be found in the epithelial cell membrane and therefore be amenable to potentiation by ivacaftor. Other CF patient populations either do not or would not be predicted to benefit from ivacaftor because the causative mutations disrupt transcription of the gene (type I) or translation of the CFTR protein (type II) to the extent that the ion channel is either absent or is prematurely degraded

and, therefore not transported to the epithelial membrane where it normally resides. Patients with CF as a result of other mutations (type IV or V), while not necessarily as well tailored for treatment with ivacaftor compared to the approved gating-type mutations, have some commonalities, (the CFTR ion channel, while defective, can be found in the epithelial cell membrane), that suggest that their CFTR ion channel activity may be potentiated by ivacaftor. Cystic fibrosis as a result of having an *R117H* mutation in the *CFTR* is one such phenotype. While similar to type III, "gating mutations" in that the CFTR ion channel can be found in the epithelial cell membrane, unlike the gating mutations, the CFTR ion channel coded by the *R117H* mutation also results in a change in the 3-dimensional structure of the ion channel rather than an isolated defect in channel open/closed regulation as in the gating mutations.

Figure 1: Functional Consequesces of *CFTR* Mutations



[Source: Zielenski J and Lap-Chee T, Ann Rev Genetics, 29:777-807, 1995.

For types I and II, no functional CFTR reaches the cell membrane.
For types III, IV, and V, CFTR reaches the cell membrane but regulation is faulty, conductance is altered (channel geometry affected), or CFTR is decreased in number, respectively.

In addition, the *R117H* mutation has two main gene polymorphisms (5-T and 7-T) which modify the extent of CF disease, with 5-T presenting with more disease features, and 7-T presenting typically with less disease. As such, the clinical manifestations are highly variable, but in comparison to those mutations in which no functional CFTR is produced, the phenotype of patients with CF who have an *R117H* mutation in the *CFTR* tend to have:

- Less severe lung disease
- Lung infection with *P. aeruginosa* that is delayed or absent
- Pancreatic sufficiency
- Decreased risk of CF-related diabetes mellitus or liver disease
- Sweat chloride values that can vary from high to normal
- A better overall prognosis and longer life expectancy

Because it is less clear how a CFTR potentiator that alters channel-open probability and therefore well suited for treatment of defective ion channels as a result of faulty "gating"

regulation might work in a CF patient population in which the ion channel defect includes a 3-dimentional structural abnormality, the Division and Vertex agreed to the conduct of a clinical study designed specifically to support efficacy for this mechanistically different mutation.

Regulatory Interactions

Ivacaftor was initially approved on January 31, 2012, for treatment of CF in patients 6 years of age and older who have a *G551D* mutation in the *CFTR* gene, the subpopulation of CF patients defined by a mutation that results in faulty ion channel regulation or "gating" defect felt most likely to be responsive to CFTR potentiation by ivacaftor. Patients with a *G551D* mutation in the *CFTR* gene comprise about 4% of the total CF population (approximately 1200 persons in the US); however they represent the largest group of patients with a single "gating" mutation in the *CFTR* gene. Despite this relatively small population, through the combined efforts of Vertex and the Cystic Fibrosis Foundation therapeutic drug development network, a robust clinical program consisting of 2 randomized, double-blind, placebo-controlled clinical trials in over 250 CF patients with a *G551D* mutation in the *CFTR* was able to be conducted.

Based partially on the results from the *G551D* program, Vertex applied for and received FDA Breakthrough Therapy (BT) designation for ivacaftor on November 13, 2012, for the treatment of CF in patients with other *CFTR* "gating" mutations felt to be functionally similar functional to the *G551D* mutation and for a different kind of mutation in the *CFTR* that results in some residual CFTR channel function being maintained to which the *R117H* mutation belongs. Development under the BT program resulted in ivacaftor being approved on February 21, 2014, to treat CF in a very small subpopulation of patients defined by having at least one of 8 additional "gating" mutations in the *CFTR* gene. The Agency subsequently had multiple meetings with Vertex to discuss the design of a clinical program to assess the safety and efficacy of ivacaftor for a CF patient population defined by mutations like *R117H* which results in an chloride channel that has functional differences from that of the "gating" mutations for which ivacaftor has been approved. Similar to the "gating" mutation program, the *R117H* mutation population represents the largest group of CF patients with a single "residual function" mutation in the *CFTR* gene (about 3% of the CF population). Because the *R117H* mutation population is large enough such that a conventional clinical study could be conducted, it was thought that it was an appropriate population to test the hypothesis that ivacaftor would be able to demonstrate efficacy in a class of mutations that have some functional differences from the strictly gating mutations for which ivacaftor has been approved

A Pre-NDA meeting was held on March 12, 2014, during which time high level summary data from Study 110 were presented. The results showed that Study 110 did not meet its primary endpoint; change in absolute percent predicted FEV1 from baseline through the 24 week treatment period, but did demonstrate a significant decrease in the pharmacodynamic endpoint, sweat chloride, and improvement in respiratory symptoms. The Division also noted the variability of the CF patient population with regard to age, poly-T tract status, baseline lung function, and baseline sweat chloride and that the study had been terminated prematurely for reasons that were not communicated by Vertex to the Agency at the time the study was stopped. Noting the failure to meet the primary endpoint for the full study population, Vertex conducted additional analyses on various subpopulations in the study and noted that adult patients appeared to have a better drug response possibly based on the fact that they had worse

lung function than younger CF patients and proposed submission of a sNDA asking for limited approval of ivacaftor to adult (≥18 yrs) patients with CF and a *R117H* mutation in the *CFTR* gene. The Division noted that typically such subpopulation analyses, while maybe pre-specified as demographic and baseline characteristic assessments were several of many identified endpoints, and were not characterized as primary or key secondary endpoints and, thus, would typically be viewed as exploratory Given that there were sufficient patients in the *R117H* mutation CF patient population to be able to study, the Division recommended the conduct of a second small clinical trial in the study population felt to be most able to respond to treatment to confirm the results of the subpopulation analyses. A less optimal alternative would be to submit the complete study results and interpretation in a sNDA.

Vertex has now submitted this current ivacaftor sNDA for the treatment of cystic fibrosis (CF) in patients ages 6 years and older who have a *R117H* mutation in the *CFTR* gene, the proposed indication we will be discussing on October 21st.

III. Product Information

Ivacaftor, trade name Kalydeco, is an approved marketed product supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor and the standard compendial excipients colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. No new CMC data was required or submitted with this application.

IV. Nonclinical Pharmacology and Toxicology

No new nonclinical pharmacology or toxicology data were required or submitted with this sNDA.

V. Clinical Pharmacology

The general clinical pharmacology and biopharmaceutics considerations for ivacaftor were addressed in the original NDA submission. Limited clinical pharmacology data were submitted with this application that demonstrate comparable pharmacokinetics between patients with CF and a *R117H* mutation in the *CFTR* gene to that for patients with CF for whom ivacaftor is approved for use.

VI. Clinical/Statistical- Efficacy

The key clinical studies submitted to support approval of ivacaftor for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene are shown in Table 2 below. The design and conduct of these studies are briefly described below, followed by efficacy and safety findings and conclusions.

Table 1: Studies Relevant to the Ivacaftor *R117H* Program

Study No.	Description	Subjects	Design	Dose	Duration	Endpoints
110 US/EU July 2012-October 2013	P3 safety and efficacy	69 CF patients ≥ 6 years of age with an *R117H* mutation	R, DB, PC, PG	150 mg ivacaftor tablets BID Placebo BID	24 weeks	FEV_1 through 24 weeks CFQR-R Sweat Chloride BMI CF Exacerbations
112[a] US/EU ongoing	Long term safety	65 CF patients ≥ 6 years of age with an *R117H* mutation	Open label	150 mg ivacaftor tablets BID	12-week interim data	Trough FEV1 CFQR-R Sweat Chloride BMI CF Exacerbations

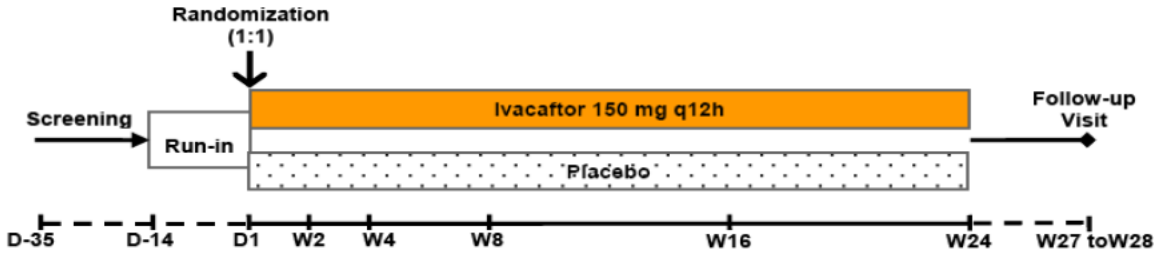
a : Patients from 2 other studies in CF patients (Studies 111 and 113) are also allowed to rollover into Study 112. The data presented are restricted to patients enrolled in Study 112.
R=randomized, DB = double-blind, PC = placebo-controlled, PG = parallel group
[Source: NDA 203188, S014, Module 5.2, Tabular Summary of All Clinical Studies]

Study Design

Study 110

Study 110 was a randomized, double-blind, placebo-controlled, parallel group study conducted in patients with CF with an *R117H* mutation in the *CFTR* gene. The study design was very similar to the phase 3 studies conducted for the original *G551D* mutation program (Studies 102 and 103, Figure 2]. After a 2-week run-in period, eligible patients were randomized 1:1 to receive ivacaftor oral tablets 150 mg or placebo twice daily for 24 weeks. Efficacy assessments, safety, and pharmacokinetic assessments were conducted on visits at weeks 2, 4, 8, 16, and 24. The Week 24 visit also included scheduling an ophthalmologic evaluation for patients 6-11 years of age which was to be completed between week 24 and the follow-up visit (3-4 weeks after the last dose of study drug).

Figure 2: Study 110 Design



D: Day; q12h: every 12 hours; W: Week
[Source: Module 5.3.5.1, CSR for Study VX11-770-110, Section 9.1, page 54.]

A diagnosis of CF was confirmed/defined as a patient having defined as a sweat chloride >60mmol/L or 2 CF-causing mutations and sinopulmonary disease. All patients had at least one *R117H CFTR* mutation. Other notable study inclusion criteria included a population ages

6 years and older, a FEV1 40-90% percent predicted for patients ≥12 years, and 40-105% for patients 6-11 years. Patients who had abnormal laboratory studies (Hgb, LFTs, GFR), chronic pulmonary infection with Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus, or had used CYP 3A inducers or inhibitors within 14 days of Study Day 1 were excluded. Patients were allowed to use all concomitant CF therapies as long as these had been initiated at least one month prior to Study Day 1. Study enrollment was planned for a minimum of 40 and a maximum of 80 patients, with estimated study power calculated based on results from Studies 102 and 103 for the original *G551D* mutation program, and a review of the CF literature. An Interim Analysis for safety and efficacy was planned after 40 patients had reached week 8. There was a plan for enrollment to stop early if a strong treatment effect was observed at the interim analysis. The interim efficacy assessment was conducted by a data monitoring committee (DMC), independent of Vertex, composed of members of the Cystic Fibrosis Foundation Data Safety Monitoring Board. Type I error rate was to be adjusted for early stopping of enrollment, if applicable.

The primary efficacy endpoint for the study was the absolute change in percent predicted FEV1 from baseline through the 24-week treatment period conducted on the full analysis set (FAS), defined as all randomized patients who received at least one dose of study drug. The primary analysis was to be based on a mixed effects model for repeated measurements (MMRM). Secondary endpoints included as absolute change in sweat chloride from baseline through week 24, absolute change in CFQ-R respiratory domain (a CF-specific patient reported outcome that assesses respiratory symptoms) score from baseline to week 24, absolute change in body mass index (BMI) through week 24, and time to first pulmonary exacerbation through week 24.

Study 112
Study 112 is an open-label long-term safety study in which CF patients from several ivacaftor clinical studies (Studies 110, 111, 113) could roll-over into. Relevant to CF patients with a *R117H* mutation in the *CFTR* gene enrolled in Study 110, all patients were given the opportunity to enroll in Study 112 at the Follow-up visit for Study 110 (about 3-4 weeks after the end of the Study 110 treatment period). Study visits were scheduled at 2 weeks and 12 weeks after beginning open-label treatment with ivacaftor and every 12 weeks thereafter. The ultimate duration of the safety study will be 2 years. Evaluations included assessing for adverse events and safety laboratory assessments. Assessments of efficacy were also made and, for this sNDA submission, reported as changes from baseline to week 12 for absolute percent predicted FEV1, sweat chloride, and CFQ-R respiratory domain.

Efficacy Results

Study 110 Disposition and Demographics
A total of 70 patients were randomized at 27 study sites in the North America and Europe; 34 to receive ivacaftor and 36 placebo. One patient received no treatment leaving 69 patients in the full analysis set. A total of 10 patients discontinued study treatment early, 8 (4 ivacaftor, 4 placebo) as a result of Vertex' decision to terminate the study early and one each due to pregnancy and non-compliance (both ivacaftor group). Patient demographics were similar between ivacaftor and placebo treatment groups, approximately 55% were male, mean age was

31 with a range of 6 to 68 years. The majority of patients were adult (72%), there was a paucity of adolescents enrolled (2 patients, 3%) and children 6-11 comprised 25% of the study population (17 total patients). Baseline sweat chloride was about 71 mmol/L and, notably the majority of patients were pancreatic sufficient (60 patients, 87%) defined as a fecal elastase-1 of ≥200 mcg/g. Table 2 below contains the description of patient demographics.

Table 2: Study 110 Patient Demographics

Variable	Placebo N=35	Ivacaftor N=34	Total N=69
Sex, n (%)			
Male	15 (43%)	15 (44%)	30 (44%)
Female	20 (57%)	19 (56%)	39 (56%)
Age (years)			
Mean (SD)	32.7 (17)	29.2 (17)	31.0 (17)
Minimum, Maximum	6, 68	6, 55	6, 68
Age Group-years, n (%)			
6-11 years	8 (23%)	9 (27%)	17 (25%)
12- 17 years	1 (3%)	1 (3%)	2 (3%)
≥18 years	26 (74%)	24 (70%)	50 (72%)
Percent Predicted FEV1, Baseline			
Mean (SD)	70 (19)	76 (19)	73 (19)
Minimum, Maximum	37, 103	33, 106	33, 106
FEV1 Group, n (%)			
<70%	15 (43%)	13 (38%)	28 (41%)
70-90%	14 (40%)	14 (41%)	28 (41%)
>90%	6 (17%)	7 (21%)	13 (18%)
BMI (kg/m^2)			
Mean (SD)	23.1 (6.0)	24.5 (6.2)	23.8 (6.1)
Minimum, Maximum	13.6, 37.8	14.4, 42.9	13.6, 42.9
Pseudomonas aeruginosa Infxn, n (%)			
Yes	19 (54%)	15 (44%)	34 (49%)
No	16 (46%)	19 (56%)	35 (51%)
Pancreatic Sufficiency Status Fecal elastase-1, n (%)			
Insufficient (<200µg/g)	5 (14%)	2 (6%)	7 (10%)
Sufficient (≥200 µg/g)	28 (80%)	32 (94%)	60 (87%)
Missing value	2 (6%)	---	2 (3%)
Geographic Region, n (%)			
North America	30 (86%)	24 (71%)	54 (78%)
Europe	5 (14%)	10 (29%)	15 (22%)
Sweat Chloride, mmol/L[a]			
N	35	32	67
Mean (SD)	73.4 (20)	67.3 (19)	70.5 (19)
Minimum, Maximum	22.5, 108.8	23.3, 120	22.5, 120

a= Baseline sweat chloride was not collected for two patients at the time of randomization
[Source: Module 5.3.5.1 CSR for Study 110, Section 10.2.1.1, Table 10-2]

As part of its responsibilities, the DMC conducted planned reviews of the study data. The DMC reviewed the unblinded interim analysis results for safety and efficacy after 40 subjects had completed the Week 8 Visit. The interim analysis included an efficacy assessment in order to determine whether further enrollment could be stopped due to strong efficacy results. Based on the results and rules pre-specified by Vertex, the DMC provided guidance on whether further enrollment could have been stopped due to strong efficacy results. The DMC recommended the study to proceed as planned, i.e., continue enrollment.

Primary and Endpoint: FEV1
Study 110 failed to meet its primary efficacy endpoint, the absolute change in percent predicted FEV1 from baseline through the 24-week treatment period. The change from baseline for patients who received placebo and ivacaftor was 0.46 % and 2.6%, respectively, resulting in a 2.1% increase in percent predicted FEV1 treatment effect (p=0.198). The treatment effect compares to the 10-12% increase in percent FEV1 compared to placebo observed in the *G551D* mutation CF subpopulation for which ivacaftor is approved.

Secondary Endpoints
Secondary endpoints for the study included assessments of the CF pharmacodynamic endpoint, change in sweat chloride, respiratory symptoms measured by the CF-specific patient-reported outcome CFQ-R respiratory domain, body mass index, and time to first pulmonary exacerbation. These endpoints have been previously used to assess the efficacy of ivacaftor in the *G551D* mutation CF subpopulation where each outcome measure supported the primary efficacy analysis (FEV1).

Sweat Chloride
Sweat chloride level is felt to be diagnostic of CF when values are ≥60 mmol/L in the context of a patient with a constellation of symptoms consistent with CF. For the ivacaftor development program it has been used as an in vivo pharmacodynamic assessment of CFTR ion channel activity in which a reduction would indicate increased channel activity. It is not known, however, how reductions in sweat chloride as a result of treatment with ivacaftor relate to clinical beneficial effects. However, as a generally accepted marker of the CFTR ion channel activity, a lack of response in sweat chloride to an intervention would suggest a subsequent lack of clinical benefit.

For Study 110, patients who received ivacaftor demonstrated a significant reduction in sweat chloride compared to placebo. Baseline mean sweat chloride values were 67 mmol/L and 73 mmol/L for the ivacaftor and placebo treatment groups, respectively. Treatment with ivacaftor resulted in a mean reduction in sweat chloride of -26 mmol/L while sweat chloride in the placebo group decreased by -2 mmol/L, resulting in a mean treatment effect of -24 mmol/L. This represents an approximately 35-40% reduction in sweat chloride compared to an approximately 50% reduction in patients with a *G551D* or other gating mutation in the *CFTR* gene for which ivacaftor is currently approved (Appendix Table 1).

CFQ-R
The CFQ-R is a disease-specific, patient reported, health-related quality of life measure for cystic fibrosis that is a commonly used patient reported outcome measure (PRO) used in CF

studies. For clinical studies conducted by Vertex, the respiratory domain of the CFQ-R has been used because it assesses respiratory symptoms that are clinically relevant to patients with CF such as cough, wheeze, congestion, sputum production, and difficulty breathing.

Treatment with ivacaftor resulted in a statistically significant improvement in CFQ-R Respiratory Domain compared to patients treated with placebo (treatment difference of 8.4 points, (95% CI: 2.17, 14.61).

The minimally important difference (MID) for the instrument has been reported as 4 points. However, the interpretability of the CFQ-R for this study population is not completely certain given that the MID was calculated based on CF program for inhaled antibiotics in patients chronically infected with Pseudomonas aeruginosa (PA) while only about 50% of CF patients enrolled in Study 110 were chronically colonized/infected with PA.

BMI

There was no significant change in BMI in ivacaftor treated patients compared to placebo over the 24 week study period (treatment difference for the mean rate of change from baseline through week 24 was 0.26 kg/m^2 (95% CI: -1.5698, 2.0950). This contrasts to 2.8 and 1.9 kg gain in weight (and corresponding increase in BMI) for patients at 24 weeks in Studies 102 and 103 for the *G551D* mutation program (Appendix Table 1). However, it should be noted that the majority of patients enrolled in Study 110 were pancreatic sufficient.

Time to First Exacerbation

There was no significant difference in time to first exacerbation between patients treated with ivacaftor compared to those who received placebo (hazard ratio 0.93). Pulmonary exacerbations in patients with CF generally occur more often in patients with more significant lung disease and the overall population for Study 110 had greater baseline FEV1 (73%) than other those in Study 102 for the *G551D* CF mutation subpopulation (64%) in which the hazard ratio for time to first exacerbation at 24 weeks was 0.40 (Appendix Table 1).

Subpopulation Analyses

Due to failure of meeting the primary endpoint and the variability of the baseline characteristics of the full population, subpopulation analyses based on age, poly-T tract status, and baseline pulmonary function (FEV1) were conducted (Table 3). It is notable that all patients demonstrated a significant (about 35-40% from baseline) reduction in sweat chloride, a pharmacodynamic endpoint reflective of CFTR ion channel activity. In addition, the adult subpopulation appeared to demonstrate a positive response to ivacaftor treatment, reflected by both a 5% increase in FEV1 and an improvement over placebo (12 points) in respiratory symptoms as measured by the CFQ-R respiratory domain patient reported outcome measure. While the adolescent (12-17 year old) population could not be assessed due to lack of study participants, it is also notable that while the adult subpopulation's FEV1 and CFQ-R respiratory domain improved significantly with ivacaftor treatment, CF patients 6-11 years of age treated with ivacaftor significantly worsened both in terms of pulmonary function (FEV1) and respiratory symptoms (CFQ-R respiratory domain). While the company's explanation that a pediatric patient who had an exacerbation during the study may have partially skewed the results, other pediatric patients also had negative results as noted in Figure 4 of the FDA

Clinical Review. The argument that the 6-11 year old population had normal or almost normal baseline lung function and therefore would not be expected to show a response, while seeming to be a plausible explanation, is not consistent with the findings of other ivacaftor studies in which children 6-11 years of age who had FEV1 values > 90% predicted demonstrated at relatively robust 7% improvement in FEV1 over 24 weeks. While those children possessed a different mutation (*G551D*) in the *CFTR* gene and, therefore, tend to have more severe disease, any explanation for why they responded to ivacaftor treatment dramatically differently than the 6-11 year old population with an *R117H* mutation in the *CFTR* gene could not be based on baseline FEV1.

Other subpopulation analyses also demonstrated differences in response to ivacaftor treatment. For example, CF patients who displayed the 5-T polymorphism also demonstrated improved lung function and respiratory symptoms to the same extent as the adult subpopulation. In contrast to the 6-11 year old subpopulation, at least some CF patients with the 7-T polymorphism, while not demonstrating any lung function benefit, appeared to have improved respiratory symptoms, although the confidence intervals are very wide. Analyses based on lung function demonstrated a worsening in FEV1 in CF patients with normal lung function (FEV1 >90% predicted) which would be expected given that majority (70%) of CF patients with FEV1 > 90% predicted were patients in the 6-11 year age group. However, patients with baseline FEV1 70-90% and < 70% predicted demonstrated about a 3% and 4% improvement in FEV1, respectively.

Table 3: Efficacy and Pharmacodynamic Endpoint Results for Study 110 *R117H* Mutation Subpopulations

Sub-population	Sweat Chloride (mmol/L)		FEV1 (% predicted)		CFQ-R Respiratory Domain (points)	
	n Iva/Pcbo	Difference from Placebo (mean)	n Iva/Pcbo	Difference from placebo (mean)	n Iva/Pcbo	Difference from placebo (mean)
>18yo[a]	22/26	-22 -26.46, -17.28	24/26	5.0 1.15/8.78	24/26	12.6 5.02/20.25
6-11	8/8	-28 -37.16, -18.10	9/8	-6.3 -12.00, -0.71	8/7	-6.1 -15.68, 3.41
5T#	13/24	-24 -30.16, -18.18	14/24	5.3 1.27, 9.32*	14/24	15.3 7.67, 22.98
7T#	10/5	-24 -33.86, -14.32	11/5	0.20 -8.14, 8.53	11/5	5.2 -12.94/23.41
FEV1 <70%	12/15	-26 -31.8, -19.3	13/15	4.0 -2.1, -10.2	13/15	11.4 1.2, 21.6
FEV1 70-90%	14/14	-20 -26.9, -13.0	14/14	2.6 -2.3, 7.5	14/13	8.8 -2.6, 20.2
FEV1 >90%	6/6	-27 -39.5, -14.1	7/6	-4.3 -9.9, 1.3	6/6	-0.7 -10.4, 9.0

*through week 24
confirmed Poly-T status

Sources: Table 16; NDA 203-188 supplement-14, CSR Study 110; March 12, 2014 meeting package, additional data submission 07/03/2014

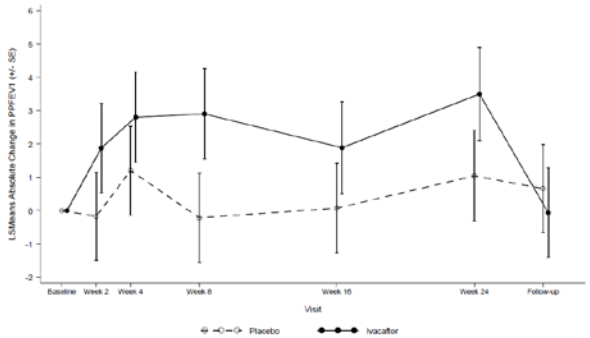
Supportive Analyses

Clinical assessments conducted during the last day of study drug treatment for Study 110 compared to those after a 3-4 week wash-out period at the follow-up visit as well as Study 112 baseline off treatment values compared to those obtained when open label ivacaftor treatment was initiated were submitted to provide supportive efficacy information.

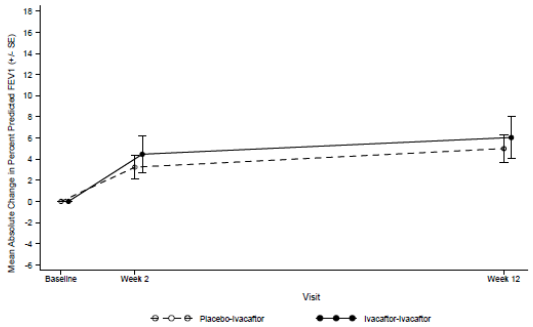
For the full Study 110 population, wash-out from ivacaftor treatment after 24 weeks' treatment resulted in a decrease in FEV1 toward baseline value consistent with withdraw from an active treatment (Figure 3 A). For Study 112, also consistent with a positive treatment effect, reinitiating open label ivacaftor treatment resulted in an increase in FEV1 over the 12 week interim analysis period Figure 3 B).

Figure 3: A: Study 110 Absolute Change from Week 24 to Follow-up Visit (Washout) in Percent Predicted FEV1; B: Absolute Change from Study 112 Baseline in Percent Predicted FEV1

A



B

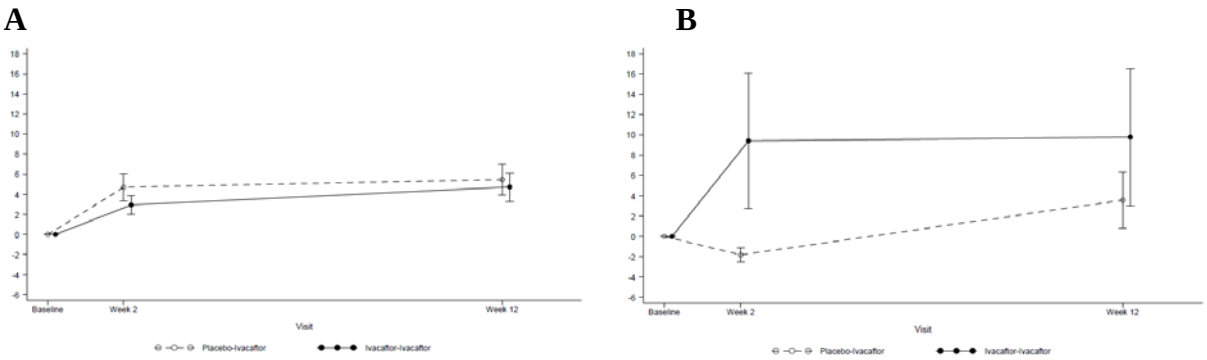


Source: A: Figure 14.2.1.3 Study 112 CSR, p. 1544 of 2633; B: Figure 4.1 Study 112 Week 12 interim analysis, p. 21 of 173

Similar effects were observed for change in sweat chloride and change in CFQ-R respiratory domain, a measure of respiratory symptoms.

When looking at subpopulations based on age, the FEV1 data from Study 112 are more variable consistent with the age-based difference in response observed in Study 110. While the ≥ 18 year old subpopulation groups demonstrated a similar modest increase in FEV1 regardless of whether they were in the placebo or ivacaftor group in Study 110 (Figure 4 A), the response in the 6-11 year old subpopulation differed based on whether treated with placebo or ivacaftor in Study 110 (Figure 4 B). Overall, however, it appears the FEV1 response to ivacaftor in the 6-11 year old subpopulation in Study 112 was relatively flat.

Figure 4: A: Study 110 Absolute Change from Baseline in Percent Predicted FEV1 for Patients Ages ≥ 18 Years (A) and 6-11 Years (B)



Source: Study 112 Week 12 interim analysis Figure 14,2,1,3, p. 161 of 173 (A) and Figure 14.2.1.2, p. 160 of 173 (B)

Summary of Efficacy

While Study 110 did not meet its primary endpoint, change in FEV1 compared to placebo through 24 weeks of treatment (2% difference from placebo), the overall study population of CF patients who received ivacaftor demonstrated a significant decrease in sweat chloride (-24 mmol/L) and improvement in respiratory symptoms (mean change in CFQ-R respiratory domain of 8.4). There was no significant difference in BMI or exacerbations between ivacaftor and placebo treatment groups for the overall population or any subpopulations. Other subpopulation analyses showed variable results. Analyses based on age demonstrated an improvement in FEV1 of 5% and improvement in CFQR-R of 12.6 in patients 18 years of age and older while children 6-11 years of age demonstrated quite the opposite response in both FEV1 and CFQ-R respiratory domain that is difficult to explain based on either outliers or lack of lung disease. Data were not available obtained that would shed light on efficacy in adolescent patients 12-17 years of age.

Subpopulations based on poly-T tract showed an improvement in FEV1 of 5% and improvement in CFQR-R of 15.3 in patients with confirmed 5T poly-T status (3% improvement in FEV1in patients with confirmed and derived 5-T status combined. While patients with 7-T status had no improvement in FEV1, the CFQ-R respiratory domain improved. Analyses based on lung function showed an improvement in FEV1 of 4.0% and 2.6% predicted in patients with baseline FEV1 of <70% and 70-90% predicted, respectively and a decrease in FEV1 of 4.3% in patients with baseline FEV1 >90% predicted (not unexpected given that most CF patients with relatively normal lung function were in the 6-11 year age group. An improvement in CFQR-R of 11.4 and 8.8 in patients with baseline FEV1 of <70% and 70-90% predicted, respectively was also noted.

Overall, the multiple analyses conducted appear to show that at least some CF patients with a *R117H* mutation in the *CFTR* gene demonstrate a benefit in response to treatment with ivacaftor, An important question for the PADAC to discuss on October 21st is whether the evidence is sufficient for approval of ivacaftor for the treatment of all CF patients 6 years of

age and older with a *R117H* mutation in the *CFTR* gene or for any particular subpopulation or are additional confirmatory data needed.

VII. Clinical/Statistical- Safety

Database
The overall safety assessment for ivacaftor is derived primarily from placebo-controlled safety data from clinical trials up to 48 weeks duration in approximately 350 CF patients previously submitted and reviewed when ivacaftor was approved in January 2012, for treatment of CF patients with a *G551D* mutation in the *CFTR* gene as well as open label safety data from CF patients exposed to ivacaftor for as many as 144 weeks. New safety information included in this submission included that from Study 110 and the open label extension (Study 112) described above.

With regard to Study 110, there were no deaths reported and there were relatively few SAEs, 6 and 4, for the placebo and ivacaftor groups, respectively over the 24-week treatment period. Consistent with the overall ivacaftor safety database, the most common SAE was CF exacerbation, with 6 and 3 being reported in the placebo and ivacaftor treatment groups, respectively. Other SAEs included cellulitis and constipation, both reported once in patients treated with ivacaftor. Common adverse events for both treatment groups were consistent with those commonly observed in the CF population such as exacerbation, increased sputum, cough, headache, diarrhea, and abdominal pain (see current Kalydeco prescribing information). In the original ivacaftor development program, liver enzyme abnormalities were observed. Regarding Study 110, there were no substantial differences between placebo and ivacaftor treated patients in the number or severity of patients who reported elevated liver enzymes. The potential for cataracts was identified in the ivacaftor program after initial approval in the *G551D* mutation population, on the basis of nonclinical findings of lens opacities in juvenile rat studies. Regarding Study 110, there were no clinically relevant changes in ophthalmologic exams, and no reports of cataract development.

Summary of Safety
Overall, the safety data for Study 110/112 do not reveal any new safety concerns. There is no reason to expect that the safety profile would be different in CF patients with a *R117H* mutation studied in Study 110 compared to CF patients with *G551D*, other gating mutations for which ivacaftor is approved, or CF patients with a *delta F508* mutation in the *CFTR* gene in which ivacaftor has been studied. There were no data that raised concerns over increased liver transaminases or other liver injury in patients receiving ivacaftor. There were no reports of CF patients developing cataracts or lens opacities during Study 110, although 24 weeks is a relatively short evaluation period for cataracts and evaluations continue.

VIII. Summary
The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by Vertex Pharmaceuticals to support the approval of ivacaftor oral tablets 150 mg twice daily for the treatment of cystic fibrosis in patients age 6 years and older who have a

R117H mutation in the *CFTR* gene. This is an important discussion in light of the limited population and variability of both the clinical presentation of and efficacy data in cystic fibrosis patients with a *R117H* mutation in the *CFTR* gene. At the PADAC meeting, Vertex will present an overview of the clinical program, which will be followed by the Agency's presentation of the efficacy and safety data. Please keep in mind the following draft topics that will be discussed and deliberated upon following the presentations.

Appendix

Appendix Table 1: Efficacy and Pharmacodynamic Endpoint Results Across Ivacaftor Programs

			Treatment Effect Across Study Period				
Study population	**Study Duration**	**N**	**Sweat Chloride**	**FEV1 % Predicted**	**CFQ-R**	**Weight/ BMI**	**Exacerbation.**
102 *G551D* ≥12yo	24 wk[a]	213	-48 (-51, -45)	10.6% (8.6, 12.6)	8.1 (4.7, 11.4)	+2.8kg (1.8, 3.7)	RR=0.4[b] (0.23, 0.71)
103 *G551D* 6-11yo	24 wk[a]	52	-54 (-62, -47)	12.5% (6.6, 18.3)	6.1 (-1.4, 13.5)	+1.9kg (0.9, 2.9)	NA
111 *Other Gating* ≥6yo	8wk	39	-49 (-57, -41)	13.8% (9.9, 17.6)	12.8 (6.7, 18.9)	0.66 kg/m^2 (0.34, 1.32)	NA
104 *F508del* ≥12yo	16 wk	112	-2.9 (-5.6, -0.2)	1.7% (-0.6, 4.1)	1.3 (-2.9, 5.6)	-0.16kg (-1.1, -0.7)	NA
110 *R117H* ≥6yo	24wk	69	-24 (-28, -19.9)	2.1% (-1.1, 5.3)	8.4 (2.2, 14.6)	0.26 kg/m^2 (-1.6, 2.1)	HR=0.93[c]

a= Study primary efficacy was to week 24, but blinded data out to 48 weeks supported efficacy
b= relative risk of exacerbation
c= time-to-first exacerbation, hazard ratio
[Sources: Ivacaftor patient labeling; NDA 203-188 Primary clinical review dated Jan 17, 2012 and Primary Statistical Review Jan 13 2012, Table 16; NDA 203-188 supplement-14, CSR Study 110; SD-258 additional data submission 07/03/2014]

Draft Topics for Discussion

1. Discuss the efficacy data for ivacaftor oral tablets 150 mg twice daily to support the proposed indication of treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene. Consider the following issues in the discussion: primary analyses, subgroup analyses based upon age, baseline FEV1, and poly-T status, and the impact of the known mechanism of action of ivacaftor and the demonstrated efficacy in other CF subpopulations on interpretation of *R117H* mutation efficacy data.

2. Do the efficacy data provide substantial evidence of a clinically meaningful benefit for ivacaftor oral tablets 150 mg twice daily for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene?

- *If not, what further data should be obtained?*

3. Discuss the safety data for ivacaftor oral tablets 150 mg twice daily.

4. Are the safety data from the overall ivacaftor cystic fibrosis program sufficient for approval of ivacaftor 150 mg twice daily for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene?

- *If not, what further data should be obtained?*

5. Do the data support approval of ivacaftor oral tablets 150 mg twice daily for the treatment of cystic fibrosis in patients age 6 years and older who have a *R117H* mutation in the *CFTR* gene?

- *If not, what further data should be obtained?*

Clinical Briefing Document for the Pulmonary Allergy Drugs Advisory Committee Meeting

October 21, 2014

Ivacaftor Oral Tablets (Kalydeco) NDA 203188

Dose: one tablet (150 mg) twice daily

Proposed indication:
"Treatment of patients with cystic fibrosis 6 years of age and older with a *R117H* mutation in the *CFTR* gene"

Reviewer: Kimberly Witzmann, MD

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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1 Introduction and Regulatory Background

1.1 Product Information

This supplemental New Drug Application (NDA) is submitted in support of ivacaftor at a chronic dose of 150mg twice daily for the treatment of cystic fibrosis (CF) in patients aged 6 years and older with an *R117H* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

Ivacaftor (trade name Kalydeco®) is an orally-available small molecule which targets one type of underlying defect in the CFTR protein which causes cystic fibrosis (CF). Ivacaftor is a potentiator of the CFTR protein, a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein.

1.2 Brief Clinical Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease that affects approximately 30,000 children and adults in the United States[1], and approximately 70,000 children and adults worldwide[2]. Approximately one in 3,500 children in the United States is born with CF each year, and CF affects all ethnic and racial groups, although is most common in Caucasians. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is the mid-to late-30's[1, 9].

In 1989, researchers discovered the gene that caused CF[3], which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR protein is an epithelial chloride ion channel, which aids in the regulation of salt and water absorption and secretion throughout the body. Lack of properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the inability to mobilize tenacious respiratory secretions, leading to recurrent infections and lung damage. While CF affects most organ systems in the body, the majority of morbidity and mortality from cystic fibrosis results from its effects in the lungs[4]. The lack of normally functioning CFTR causes abnormal chloride secretion and water reabsorption, leading to dehydration of the airway surface liquid and impaired mucociliary clearance. Over time, the CF lung is exposed to a vicious cycle of infection, inflammation, and damage, which causes progressive and irreversible airways obstruction, bronchiectasis, and ultimately respiratory failure[5, 6].

Mutations in the CFTR gene result in reductions in quantity, quality, or both, of the CFTR proteins. In order to have CF disease, one must have two mutations in the *CFTR* gene, since the disease is autosomal recessive. To date, almost 2,000 mutations in *CFTR* have been identified[10]. Historically, these mutations have been classified into

groups by their effect on CFTR protein (Classes I-V). For Classes I and II, little to no functional CFTR reaches the cell membrane. For the other groups, CFTR reaches the cell membrane but regulation is faulty (Class III), pore/channel geometry is wrong (Class IV), or CFTR is decreased in number (Class V).

In the United States, approximately 90% of patients carry at least one (Class II) *F508del* allele[1], with 60-70% of patients being homozygous for the *F508del* mutation. Worldwide, approximately 4% of patients carry the *G551D* (Class III) mutation[1, 8], and another 1% of patients carry other Class III mutations. The Class IV mutations, (of which *R117H* is the most prevalent), accounts for roughly 2-3% of the CF population[1].

Agents that increase the chloride ion transport properties of the CFTR channel have been termed "potentiators" in the literature. Ivacaftor is one such drug, which has been shown to increase chloride ion transport across the CFTR chloride channel in epithelial cell membranes; it is the only commercially-available drug that alters CFTR channel function. It is currently approved in the US for the treatment of patients with CF, defined by having one of nine functionally related mutations in the CFTR (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*). These mutations have in common the fact that they all fall into a category of mutation called the Class III "gating mutations"[7] which reflect the CF population initially predicted to best benefit from ivacaftor, i.e., those patients with mutations where the resultant abnormal CFTR ion channel has faulty ion regulation, but can be found in the epithelial cell membrane, and therefore be amenable to potentiation by ivacaftor. Other CF patient populations either do not or would not be predicted to benefit from ivacaftor, because the causative mutations disrupt transcription of the gene (Class I) or translation of the CFTR protein (Class II) to the extent that the ion channel is either absent or the protein is prematurely degraded, and therefore not transported to the epithelial membrane where it normally resides. Patients with CF as a result of other mutations (Class IV or V) share some commonalities with the Class III defects (the CFTR ion channel, while defective, can be found in the epithelial cell membrane), which suggest that their CFTR ion channel activity may be potentiated by ivacaftor. The defective *R117H*-CFTR protein is one such example. While similar to the Class III "gating mutations," in that the CFTR ion channel found in the epithelial cell membrane displays faulty gating regulation, it also demonstrates conductance defects (likely due to conformational changes in pore geometry and/or charge at the mouth of the ion channel)[14, 23, 24].

Vertex has expanded their ivacaftor development program to evaluate the use of ivacaftor in this new population of patients with the *R117H* mutation in CFTR, since this mutation is known to produce a CFTR protein with a conformational change that leads to conductance defects, as well as demonstrates decreased channel-open times as compared to normal CFTR protein channels[14]. Mutation classes which produce CFTR protein that is integrated into the epithelial cell membrane may have a more variable clinical presentation, in part because some are able to demonstrate partial chloride transport. For example, from the Sponsor's *in vitro* studies (which utilized *R117H-5T*), the *R117H-CFTR* gating defect has a channel-open probability 22% of normal, as

compared to the *G551D-CFTR* defect, which has only a 3% channel-open probability. In addition, other *CFTR* gene polymorphisms can impact the clinical phenotype displayed by patients with CF, because of effects on mRNA splicing. The *cis*-configuration of an associated poly-T region of intron 8 of *CFTR* is critical to further modify the expression of CF disease[11]. These poly-T regions generally have 5, 7, or 9 thymidine repeats that influence splicing of exon 8 to 9. For the *R117H* mutation, having an associated *cis*-poly-5T polymorphism causes reduced splicing of mRNA in exon 9, which leads to approximately 90% decreased expression of full-length *CFTR* gene products[19], such that *R117H* with 5T in the *cis*-configuration is considered a disease-causing CF mutation. *R117H* with 7T in *cis*-configuration is associated with less severe disease, and is considered less likely to be a disease-causing mutation, even when in the presence of a second disease-causing mutation[12]. Therefore, levels of CFTR mRNA depend on genotype determining the length of the poly-T sequence in intron 8, the presence of CFTR mutations, or both[13].

1.3 Currently Available Treatments for Proposed Indication

Ivacaftor is currently approved in the US for the treatment of patients with CF defined by having one of nine functionally related (faulty ion channel regulation) mutations in the CFTR (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*).

There are no other drugs available that are directed at the cause of cystic fibrosis (i.e., the absent or defective CFTR ion channel), but a number of drugs are used to treat the symptoms and sequelae of the disease. Listed below are drugs commonly used for the treatment of CF and its complications, including those with FDA-approved indications as well as those with commonly used off-label. This list is not exhaustive, but is rather meant to address the most common categories of medications typically utilized by patients with CF.

Table 1: Drugs Commonly Used for the Treatment of Cystic Fibrosis

Active Ingredient	Trade Name	FDA-approved for CF Indication?
Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa		
Tobramycin (nebulized)	TOBI	Yes
Tobramycin (dry powder)	TOBI Podhaler	Yes
Aztreonam (nebulized)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
Inhaled Treatments used as Mucolytics		
Dornase alpha (DNase)	Pulmozyme	Yes
Hypertonic Saline (7%)	HyperSal 7	No
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase™	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air HFA, Ventolin HFA, Proventil-HFA, etc.	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Anti-Inflammatory Agents		
Oral azithromycin	Zithromax	No
Oral high-dose Ibuprofen	Motrin, Advil, etc.	No
[Source: Approved labeling data from Drugs@FDA.gov]		

1.4 Important Safety Issues with Consideration to Related Drugs

There are currently no commercially-available, related drugs.

1.5 Availability of Proposed Active Ingredient in the United States

Ivacaftor is currently approved in the US for the treatment of patients with CF defined by having one of nine functionally related mutations in the CFTR (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*).

Ivacaftor was approved for use in patients aged 6 years and older with a *G551D* mutation on January 31, 2012, and the other 8 related mutations were approved under a supplemental NDA in February, 2014. The efficacy of Ivacaftor was demonstrated in these patient populations, and is described in approved product labeling (see accompanying current prescribing information.

1.6 Relevant Regulatory Background Information

Ivacaftor was approved for treatment of cystic fibrosis in patients 6 years of age and greater, with at least one copy of the *G551D* mutation in CFTR on January 31, 2012. The original NDA provided a reasonable rationale for benefit based on the mechanism of action of increasing CFTR channel-open probability, and demonstrated replicate evidence of efficacy (in Studies 102 and 103). Efficacy was not demonstrated in a distinct population of *F508del*-homozygous patients in Study 104; patients had a 1.7% (95%CI: -0.6, 4.1) difference in absolute percent predicted FEV1, and no clinically relevant change in sweat chloride (-2.9mmol/L, 95% CI: -5.6, -0.2).

The supplemental NDA for eight additional rare CFTR mutations (*G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R)* which demonstrate functional similarities to the *G551D* mutation was approved in February 2014, based on the knowledge that the mechanism of action in mutations similar to *G551D* would be analogous. One of these mutations, *G970R*, did not provide sufficient evidence of efficacy to allow for labeling at that time.

Throughout the ivacaftor development program, and specifically at the February 2013, Breakthrough designation meeting, the Sponsor and the Division had discussed that the intent of Study 110 would be to provide proof-of-concept for the use of ivacaftor in a distinct population of CF patients with "residual function" *CFTR* mutations, which are different functionally from those with the *G551D* mutation or related "gating" mutations. As described above, Class III mutations have altered channel-open regulation of CFTR, but *R117H* has classically been referred to in the literature as a Class IV mutation. Because in this new population (for which *R117H* is the most common mutation), the mechanism of action was less clear as to how a CFTR potentiator that alters channel-open probability might work, and there was uncertainty of its effect, the Division had previously stated that substantial clinical evidence would need to be demonstrated to support this new program.

The Division received a Type B meeting request on December 19, 2013, to discuss results from Study 110, and the expansion of the ivacaftor indication to include patients with the *R117H* mutation. On January 8, 2014, a meeting was granted, to be held on March 12, 2014. The package described that Study 110 had failed to meet its primary efficacy endpoint, absolute change from baseline in percent predicted FEV1 through week 24. However, the Sponsor proposed in the meeting package that efficacy could be derived for the indication, "treatment of CF in patients age 18 years and older who have an *R117H* mutation in the *CFTR* gene" from this data. This proposal is based on data in adult patients with an *R117H* mutation, derived from a subset analysis by age.

The Division initially replied that, while the data was suggestive of a benefit for the >18 year old subgroup, Study 110 did not meet its primary objective, such that the subgroup analyses would be considered exploratory. The Division stated that at least one additional study would be required to demonstrate efficacy of ivacaftor for patients with

CF who have a *R117H* mutation in the CFTR and who represent a new group of patients that may be responsive to ivacaftor. Alternatively, the Applicant could submit a supplemental NDA which would be reviewed. The Applicant subsequently submitted a New Drug Application on June 30, 2014, for the indication, "treatment of CF in patients age 18 years and older who have an *R117H* mutation in the *CFTR* gene."

On August 19, 2014, the Applicant submitted an amendment to the NDA to change the indication to, "treatment of CF in patients age 6 years and older who have an *R117H* mutation in the *CFTR* gene."

2 Sources of Clinical Data, Review Strategy, and Trial Design

2.1 Tables of Studies/Clinical Trials

The Applicant provides a full table of all the studies contained within this NDA. There are a total of 26 studies listed; 23 of these studies were considered in the original Application (efficacy and safety in CF patients with a *G551D* mutation), one study was reviewed under sNDA-4 (efficacy and safety in 8 additional similar CF mutations), and two studies were submitted under this supplement. One is a randomized, placebo-controlled trial, and the other presents interim data from an open-label extension. The studies are listed below.

Table 2: Studies Relevant to Clinical Regulatory Decision-Making

Study #/ year	Study Type/ Design	Study Duration	CF Population	n	Treatment Arms Ivacaftor	Study Sites
110 *2012-2013*	Efficacy and Safety R, DB, PC, PG	24 weeks	***R117H*** ≥ 6 years	69	150mg BID vs. Placebo	27 sites in the US and EU
112[a] *Ongoing*	Long-term Safety Open-label	Interim data to 12 weeks[b]	***R117H*** From Study 110 ≥6 years	65[e]	150mg BID	33 sites in US, UK, France, Belgium

a= Study 112 is enrolling patients from Study 110 as well as studies 111 and 113. It consists of two arms, an open-label treatment arm of iva 150 BID, and an observational (no iva) arm
b= This interim analysis only includes patients who rolled over from Study 110 into the treatment arm
[Source: NDA 203188, S014, Module 5.2, Tabular Summary of All Clinical Studies]

2.2 Review Strategy

The clinical development program for ivacaftor in patients with the *R117H-CFTR* mutation consists of double-blind, placebo controlled efficacy and safety data from 24

weeks' treatment in Study 110. An additional 12 weeks of open-label efficacy and safety data are also provided as an interim report of Study 112, the open-label extension study in which patients were enrolled after Study 110.

For this review, the primary data supporting efficacy in the CF population with an *R117H* mutation comes from Study 110. Given that the study failed to meet its primary endpoint, any determination of efficacy will need to rely on several factors including our understanding of the molecular genetics of CF, knowledge of how ivacaftor works, post-hoc analyses of Study 110, and previous demonstration of efficacy for other CF-causing mutations. The open-label interim efficacy data from study 112 will be reviewed briefly in the efficacy section, with a focus on the impact of off/on treatment effects on efficacy endpoints such as FEV1. The efficacy will then be described within the context of all that is known regarding ivacaftor in approved populations.

Safety of both studies will be discussed in Section 4 of this review, and explored in relation to the overall safety database from ivacaftor use in approved populations.

2.3 Dose Selection/Rationale

The approved dose of ivacaftor is 150mg every 12 hours in the 9 mutations for which it is indicated. The original NDA submission demonstrated that PK between healthy subjects and patients with CF was similar. This, in combination with efficacy and safety data from the approved indications, led the Applicant to select the same dose to be evaluated for the *R117H* population.

2.4 Clinical Trial Design

2.4.1 STUDY 110

Study Title:

Protocol VX11-770-110
"A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects with Cystic Fibrosis Who Have the *R117H-CFTR* Mutation"

Study Dates:

July 3, 2012 through October 25, 2013

Study Sites:

Subjects were enrolled at 27 sites in the US and Europe.

Description of Study

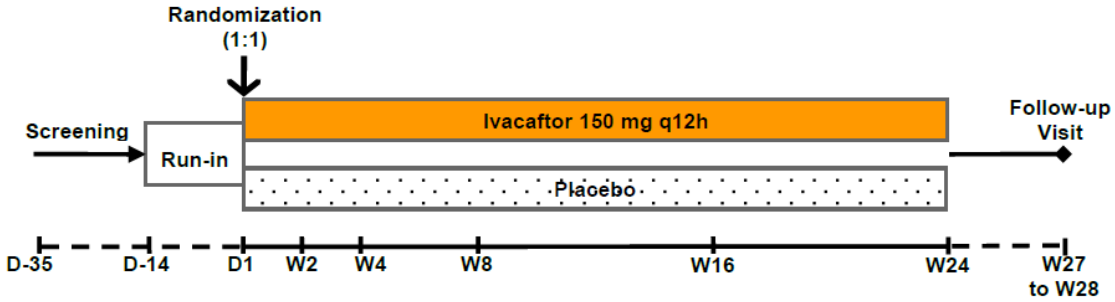
This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group multicenter study. Patients were randomized to receive either placebo or ivacaftor 150 mg BID for 24 weeks. The study included a screening period (Day -35 to Day -15), a run-in period (Day -14 to Day -1 relative to the first dose of study drug), a treatment period (first dose of study drug on Day 1, to Week 24), and a follow-up period. Study visits during the treatment period occurred on Day 1, weeks 2, 4, 8, 16, and 24. Patients who prematurely discontinued study drug treatment had an early termination visit; follow-up visit was not required if the early termination visit occurred 3 weeks or later after the last dose of study drug.

Study Schedule

The schematic for Study 110 is shown in Figure 1. All patients were initially identified within the screening period from Day -35 to Day -14, during which patients were recommended to remain on stable CF medication regimens (defined as those being followed for at least 4 weeks prior to Day 1) through the follow-up visit. Stable CF medications included the following:

- Inhaled hypertonic saline was continued through follow-up (patients not using hypertonic saline at least 4 weeks before Day 1 would remain off this treatment for the study duration)
- Single, inhaled antibiotic administered continuously was continued through follow-up
- Stable regimen of single inhaled cycled (28-day on/28-day off) antibiotic was continued through follow-up, and clinic visits on Day 1 and weeks 8, 16, and 24 should have been timed to occur at the end of an off-cycle, (no fewer than 14 days after last dose of inhaled antibiotic from the previous on-cycle)
- Subjects who were on alternating regimens of cycled antibiotics (i.e., TOBI alternating with Cayston) should have remained on their existing schedules through the follow-up visit

Figure 1: Schematic of Study Design VX11-770-110



D: day; q12h: every 12 hours; W: week.
Note: Since the study was terminated early by the sponsor, study drug was administered for periods of up to 24 weeks.
[Source: Module 5.3.5.1, CSR for Study VX11-770-110, Section 9.1, page 54.]

Screening evaluations were completed after informed consent/assent documents were signed (as applicable), at any time from Day-35 to Day -15 before first dose of study drug. Screening assessments included comprehensive history, demographics, CF genotype, review of prior and concomitant medications/ treatments, report of adverse events, physical exam, vital signs, ECG, spirometry, and clinical laboratories (including serum chemistries, hematology, coagulation and urinalysis studies), sweat chloride testing (if there was no prior documented test and if needed for inclusion), stool for fecal elastase-1, and serum pregnancy testing to female subjects of child-bearing potential). An ophthalmologic exam was required at screening, but could be completed up to randomization. Patients who met all the eligibility criteria and none of the exclusion criteria and for whom there was documented informed consent/assent as applicable, continued into the run-in period of study.

The run-in period visit occurred on Day -14 $\pm$2 days. Assessments included an abbreviated physical exam, vital signs, spirometry, review of prior and concomitant medications/ treatments, report of adverse events, optional DNA analysis, completion of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), and review of eligibility criteria.

On Day 1 of the treatment period, patients were randomized in a 1:1 fashion to receive ivacaftor 150mg or placebo, twice daily through 24 weeks. The treatment period included visits on Day 1, as well as at weeks 2, 4, 8, 16, and 24. Assessments for each visit were very similar (exceptions made for optional testing, IRT, and fecal elastase), and include the following: an abbreviated physical exam, vital signs including weight and height, review of prior and concomitant medications/ treatments, report of adverse events, completion of the CFQ-R, PK and inflammatory marker measurements, clinical laboratory assessments (including serum chemistry, hematology, coagulation studies, pregnancy testing as applicable), sputum cultures, sweat chloride testing, spirometry, and dispensing of study drug and drug counts until week 24. The Week 24 visit also included scheduling an ophthalmologic evaluation for patients 6-11 years of age (completed between week 24 and follow-up visits).

For all patients who discontinued from study drug for any reason, an Early Termination Visit was conducted as soon as possible after the last dose of study drug, with the same assessments as above, except a full physical exam was conducted, as was an ophthalmologic exam for patients 6-11 years of age. Three to 4 weeks after the last dose of study drug, patients were evaluated at a Follow-up visit; the assessments were the same as for treatment period visits, except no PK samples were obtained.

Population

The study population included patients 6 years and older with CF who have a *R117H-CFTR* mutation; patients who carry a *G551D*- or other approved mutation on their other allele were excluded.

Summary of Notable Inclusion/Exclusion Criteria

Inclusion criteria included the following:

1. Confirmed diagnosis of CF, defined as a sweat chloride ≥60mmol/L or 2 CF-causing mutations and sinopulmonary disease
2. At least one *R117H-CFTR* mutation
3. FEV1 40-90% for patients ≥12 years, and 40-105% for patients 6-11 years
4. Minimum weight of 15kg
5. All safety screening labs with no clinically significant abnormalities, per Investigator
6. Negative pregnancy test for females of child-bearing potential, and agreement of all patients to meet contraception requirements (as appropriate by age)

Exclusion criteria included the following:

1. *G551D* or other similarly functioning mutation, commonly described as a "gating defect"
2. URI or LRTI, CF exacerbation, or medication change within 4 weeks of Day 1
3. Pregnancy or breastfeeding, or planning a pregnancy
4. Any of the following test results noted at screening:
    a. Hgb <10g/dL
    b. LFTs ≥3x ULN for 3 or more of AST, ALT, Alk Phos, GGT, total bilirubin
    c. GFR ≤30mL/min/1.73m^2 if ≥18yo, or ≤45mL/min/1.73m^2 if 6-17yo
5. History of solid organ or hematologic transplant
6. Chronic infection with organisms associated with more rapid decline in pulmonary status (*B. cenocepacia, B. dolosa, M. abscessus*) at screen
7. use of CYP 3A inducers or inhibitors within 14 days prior to Day 1
8. Evidence of Cataract or lens opacity at screening
9. History of substance abuse, participation in another trial, or any other reason deemed by Investigator to affect outcome or patient safety

Reviewer's Comment:
While the definition of CF as listed above in #1 is fairly standard in clinical practice, this definition may not have been specific enough for this R117H population, because the poly-T status also plays a significant role in disease expression, and therefore in clinical phenotype. Some of the patients enrolled in the trial (as will be discussed further in Section 3) met criteria by having two CF alleles, but had sweat chloride values less than 40mmol/L at baseline, which is considered within the range of normal. Eight of the patients enrolled had a baseline sweat chloride less than 40. Thus, the decision regarding eligibility must have rested on the presence of sinopulmonary disease.

The inclusion/exclusion criteria as otherwise outlined above are appropriate.

Treatments

Study Treatments
Patients were randomized in a 1:1 ratio to receive either ivacaftor 150mg or placebo, taken every 12 hours with a high-fat meal, for up to 24 weeks. Dose modifications were not permitted, but dose interruptions were considered on an individual case basis, such as interruption for elevated liver enzymes.

Permitted and Prohibited Medications
All CF-specific treatments were allowed in this study, as long as patients had been prescribed the regimens chronically (or cycled chronically), for at least a month before Day 1. Any CYP3A inducers or inhibitors were prohibited, including herbal supplements (St. John's Wort), and dietary sources (grapefruit). Likewise, any investigational study drugs used within 30 days or 5 terminal half-lives of Study Day 1, were prohibited.

Patient Discontinuation/Withdrawal Criteria

Patients could withdraw at any time at their own request, or could be withdrawn by investigator or the Applicant. Patient withdrawal criteria included the following:

1. Female patient has confirmed pregnancy
2. Elevated LFTs with no alternate etiology:
    a. ALT or AST >8xULN
    b. ALT or AST >5xULN for >2 weeks
    c. ALT or AST >3xULN in association with Tbili>2xULN +/- jaundice
3. Vertex, regulatory authorities, or IRB close the study
4. Patient participates in another study
5. Patient develops a cataract or lens opacity

Additionally, the protocol listed reasons for which a patient may be discontinued, decided by the Investigator and medical monitor:

1. Patient develops a medical condition that requires prolonged concomitant therapy with a prohibited medication, or will have prolonged interruption
2. Patient develops life-threatening AE or SAE that places him at risk

3. Study requirement non-compliance
4. LFT elevations that do not meet criteria above

Reviewer's Comment:
Version 1 of the protocol contained the language that the Sponsor could stop the study; this standard language has not changed between versions.

Follow-up after Early Termination
The protocol states that if a patient withdraws early, the Investigator should inquire about the reason for withdrawal, and request that the patient complete the Early termination and Follow-up visits, and complete reporting of any adverse events.

Replacement Plans
No patients were to be replaced if discontinued after randomization.

Study Objectives

The objectives of Study 110 were to evaluate the efficacy and safety of ivacaftor in patients with CF who have the *R117H-CFTR* mutation.

Sample size, Enrollment, and Power
Enrollment was planned for a minimum of 40 and a maximum of 80 patients, with estimated study power calculated based on results from Studies 102 and 103 in the original program, as well as a review of the CF literature. An Interim Analysis (IA) for safety and efficacy was planned after 40 patients had reached week 8. There was a plan for enrollment to stop early if strong treatment effects were observed at the IA, using the O'Brien-Fleming stopping boundary. The protocol notes that "regardless of whether or not enrollment is stopped early, all enrolled subjects will complete the study and the final analysis will be based on data from all enrolled subject assessments." Type I error rate was to be adjusted for early stopping of enrollment, if applicable.

Efficacy Analyses
Based on the protocol, all analyses were to be based on the full analysis set (FAS), defined as all randomized patients who received at least one dose of study drug. The primary efficacy endpoint was the absolute change in percent predicted FEV1 from baseline across all visits through Week 24. The primary analysis for this endpoint was to be based on a mixed effects model for repeated measurements (MMRM). With a mixed effects model as the primary analysis model, no imputation of missing data was done. However, the protocol noted that a number of sensitivity analyses assessing the impact of missing data on efficacy evaluations would be performed. [Source: Module 5.3.5.1, Protocol VX11-770-110, v4.0, section 13.3.3.1]

Key secondary endpoints were identified as absolute change in sweat chloride from baseline through week 24, absolute change in CFQ-R respiratory domain score from baseline to week 24, absolute change in body mass index (BMI) through week 24, and

time to first pulmonary exacerbation through week 24. The pre-specified order of analyses to adjust for multiplicity was planned, such that if the primary efficacy endpoint provided a statistically significant result, BMI and sweat chloride would be evaluated, and if statistically significant results were obtained there, then CFQ-R respiratory domain and time-to-first pulmonary exacerbation would subsequently be evaluated. Additional tertiary endpoints were also to be analyzed as appropriate.

Spirometry measurements were conducted in a uniform fashion across time and study sites in accordance with procedural guidelines described in the protocols, and performed according to the American Thoracic Society Guidelines, utilizing Hankinson and Wang reference standards. All spirometry was to be collected pre-bronchodilator, if possible, defined as no SABA within 4 hours and no LABA within 12 hours. If patient forgot to hold his SABA or LABA at the screening visit, then post- bronchodilator values were recorded at screening, but all other visits collected pre-bronchodilator values. If Day 1 spirometry was measured pre-bronchodilator, but at another visit the patient forgot to withhold SABA/LABA, then the post-bronchodilator values were collected for that visit only. If patient used bronchodilator on Day 1, the Day 1 visit and all subsequent visits collected post-bronchodilator values. [Source: Module 5.3.5.1, Protocol VX11-770-110, v4.0, Section 12.5.1].

CF Pulmonary exacerbation was determined by the same definition used in the prior ivacaftor program (the “modified Fuchs’ definition”), which is widely accepted within the CF community and has also been accepted within the Vertex development programs. It is defined as a change in antibiotic therapy (IV, inhaled, oral) for any 4 or more of the following:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

Sweat Chloride samples were collected using a Macroduct® collection device, and sent to a central lab for testing.

CFQ-R is completed in the patient’s native language, if validated translations are available. It was to be completed first, before interventions occurred. Age-appropriate versions were to be completed based on age at study entry.

Reviewer's Comment:
The CFQ-R respiratory domain was also used in the original NDA as a patient-reported outcome (PRO) measurement; this is a useful tool, commonly utilized in CF clinical studies. It is a method of assessing an important clinical endpoint, i.e., how a patient is feeling and functioning, which may not directly correlate with spirometry. It should be noted, however, that the minimum clinically-important difference (MCID) of 4 points (for patients with stable disease) was determined in a study for an inhaled antibiotic product in CF patients who were all chronically infected with Pseudomonas aeruginosa, which may not necessarily reflect the patient population enrolled in Study 110.

Safety analyses included treatment-emergent AEs, clinical laboratory findings, ECG outcomes, and vital sign measurements. This will be discussed in detail in the Safety assessment.

Interim Analyses for Efficacy and Safety
A DMC, independent of Vertex, was formed using the Cystic Fibrosis Foundation Data Safety Monitoring Board. As part of its responsibilities, the DMC conducted planned reviews of the study data, as outlined in the DMC Charter.

The DMC was to review safety data after 10 patients completed 8 weeks of treatment, and recommend whether or not the study should proceed without change.

The DMC reviewed the unblinded interim analysis (IA) results for safety and efficacy after a minimum of 40 subjects had completed Week 8 Visit, and based on the results and rules pre-specified by Vertex, provided guidance on whether further enrollment could have been stopped due to strong efficacy results. [Source: Module 5.3.5.3, CSR 110, section 9.1.6, page 56]

Protocol Amendments/Conduct

Table 3: Protocol Amendments for Study 110

Conduct	Date	Major Changes Made
Version 1.0	02-08-2012	Original Version
Version 2.0	03-21-2012	• Exclusion criterion added for cataracts • Clarification added for stable maintenance of cycled antibiotic therapy • Changes made to PK section, blinding for samples • Reduced number of ECG assessments • Clarified size justification and stopping rules • Clarified optional blood draws
Version 2.0-UK	06-15-2012	• Clarification of MHRA contraceptive requirements
Version 3.2	12-18-2012	• Changed follow up after 24 weeks to include observational arm of Study 112 as well as Tx arm • Ophthalmologic exam added to safety endpoints, description of exams strengthened • Minor changes or clarifications to language and timing of assessments
Version 4.0	06-11-2013	• Removed restriction of hypertonic saline use, as long as patients remained on it through study • Clarification language added regarding early study termination • Updated statistical method for adjusting for multiplicity
[Ref: Module 5.3.5.1.3, Clinical Study Report Body 110, Section 9.8, pg. 102]		

DMC Findings

As part of its responsibilities, the DMC conducted planned reviews of the study data. The interim analysis included an efficacy assessment in order to determine whether further enrollment could be stopped due to strong efficacy results. Based on the results and rules pre-specified by Vertex, the DMC recommended that the study proceed as planned without change (i.e., continue enrollment).

Reviewer's Comment:

Study 110 enrollment was discontinued early, after 70 patients were randomized. In addition, the study itself was stopped by the Applicant, before 8 adult patients could complete to the week 24 endpoint. In contrast to the DMC recommendation, the Applicant made the decision to stop enrollment early.

Results

Efficacy results of this trial will be discussed in detail in Section 3 Integrated Review of Efficacy. Safety will be discussed within Section 4 Review of Safety.

2.4.2 STUDY 112

Study Title:

VX12-770-112
A Phase 3, Two-Arm, Rollover Study to Evaluate the Safety of Long-Term Ivacaftor Treatment in Subjects 6 Years of Age and Older with Cystic Fibrosis and a Non-*G551D* CFTR Mutation

Study Dates:

The study began on Feb 13, 2013, and the last date of results used in this interim analysis was April 25, 2014. The interim study report is dated June 6, 2014; Study 112 is ongoing.

Study Sites:

Study 112 includes 33 sites in Belgium, France, the UK, and the US.

Reviewer's Comment:
There are more sites noted for Study 112 (33) than for Study 110 (25), because Study 112 includes patients who have rolled over from 3 different clinical trials (see below). This interim data presented only reflect the roll-over of patients enrolled in Study 110.

Description of Study

Study 112 is the ongoing Phase 3, two-arm, multicenter, open-label, rollover study conducted in subjects with CF who had previously been enrolled in Study 110, as well as those from Study VX12-770-111 (Study 111; subjects with a *non-G551D-CFTR* gating mutation), or Study VX12-770-113 (Study 113; subjects who have phenotypic or molecular evidence of "residual CFTR function").

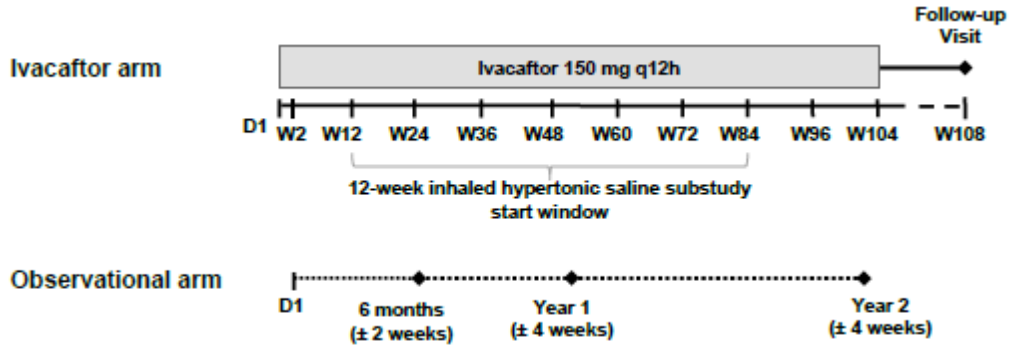
- Ivacaftor arm: Subjects who completed their assigned study drug treatment duration in Study 110 or Study 111 will be enrolled. Subjects from Study 113 who completed all study-related treatments through the Follow-up Visit and have met at least 1 of the Study 113 responder criteria during the 8-week Open-label Period in that study will be enrolled. The treatment duration will be approximately 104 weeks.
- Observational arm (for subjects from Study 110 and Study 111 only): The Observational arm is comprised of subjects who prematurely discontinued study

drug treatment and received at least 4 weeks of treatment in the previous ivacaftor study, subjects who completed the previous study and enrolled in the observational arm, and subjects who completed the previous study but did not meet the inclusion criteria of the ivacaftor arm will be enrolled.

The Interim Analysis data provided within this NDA submission as support for Study 110 does not include the entire population from Study 112, but rather provides the data only from that subset of patients who rolled over from Study 110 and continued into Study 112 (n=65), and provides interim data through week 12.

A schematic of the study design is provided below.

Figure 2: Schematic of Study 112 Design



[Source: Module 5.3.5.1, protocol for Study VX12-770-112, Figure9-1, page 29.]

Study Schedule

As noted above, patients receiving ivacaftor in an open-label fashion are evaluated at weeks 2, 12, and every 12 weeks thereafter.

All patients from Study 110 could enroll at the Follow-up visit, so had been off treatment for 3-4 weeks. All patients were initiated on ivacaftor in an open-labeled fashion. Assessments include vital signs, physical exams, safety labs, AEs, CFQ-R assessments, spirometry and PK collections. Additionally, ECGs, ophthalmologic exams, and sweat chloride results were obtained at every 24 weeks.

Population

The study population included patients 6 years and older with CF who have a *R117H-CFTR* mutation, who completed study 110 and enrolled into study 112; this is a subgroup of the total Study 112, which includes patients from Studies 111 and 113 as well.

Summary of Notable Inclusion/Exclusion Criteria

Important inclusion criteria pertinent only to those from study 110 are listed below:

1. Patients must have completed their assigned study treatment duration in the previous study.
2. Female patients must have a negative pregnancy test, as appropriate
3. New informed consent was signed

Exclusion criteria were the same as those for Study 110, including illness or condition that might confound results or place the patient at risk, pregnancy/breastfeeding, concomitant use of CYP3A inhibitors or inducers, and evidence of lens opacity/cataract.

Reviewer's Comment:
The protocol for Study 110 was modified in version 4, June 2013, to add language specifically stating that patients who were on treatment when the study stopped would be considered as having completed their treatment, so as to meet entry criteria for Study 112.

Treatments

All patients in the treatment arm received open-label ivacaftor 150mg BID. Patients in the observation arm receive no study drug.

Patient Discontinuation/Withdrawal Criteria

Patient discontinuation criteria are the same for Study 112 as for Study 110, except that an additional possible discontinuation is if ivacaftor becomes commercially available in the patient's country of origin, and is reimbursed for their specific indication.

Study Objectives

The primary objective is to study the long-term safety of ivacaftor in treated patients with CF, and to evaluate the post-treatment safety in those who enrolled in the observational arm. Additional assessments are made to assess open-label efficacy, and are the same as those primary and secondary endpoints from Study 110, namely, changes from baseline to week 12 in absolute FEV1 percent predicted, sweat chloride, and CFQ-R respiratory domain.

Interim Analyses
Per the protocol, the interim analysis (IA) for Study 112 was to be performed after 90% of all patients from both Studies 110 and 111 have completed the week 24 visit. [Source: Module 5.3.5.1, Protocol VX12-770-112, Section 13.3.5, page 56].

Instead, the Applicant has provided interim data on all patients from Study 110 only, who enrolled into Study 112, followed through Week 12. The IA evaluates the

difference from each patient's baseline Study 112 value, which are the same values measured at the follow-up visit in Study 110, after 3 to 4 weeks' washout from blinded study drug treatment. So patient data presented compares the individual off-drug values to those on open-label ivacaftor treatment. For the purposes of these interim data analyses, patients are described by their study drug treatment allocations in Studies 110 and 112, (i.e., either placebo/ivacaftor or ivacaftor/ivacaftor).

No data from Study 111 is included in the Study 112 analysis for this supplemental application.

Protocol Amendments/Conduct

Version 1 of the protocol was completed in February 2012, with the following amendments noted:

- Version 2 (March 2012), which added clarifications regarding the early termination visit and follow-up time point
- Version 2.1 (June 2012) was for the UK, clarifying contraceptive language
- Version 3.1 (December 2012) extended duration to 2 years to comply with the EU risk management plan, clarified the observation arm enrollment and objective, added ophthalmologic examinations to the protocol, and added an Interim analysis (IA) after all subjects had completed week 24
- Version 3.2 (April 2013) added inclusion of patients completing Study 113 to enrollment, with specific language regarding enrollment timing and assessments
- Version 4.0 (February 2014) added language to discontinue patients in the ivacaftor arm once commercially-available drug becomes available in their country, an optional sub-study was added (ivacaftor plus hypertonic saline), and the timing of the interim analysis changed to state that 90%of subjects (rather than all) from Studies 110 and 111 complete through week 24

Results

The results of Study 112, in regard to support of efficacy of Study 110, will be discussed in Section 3 Integrated Review of Efficacy. Safety will be discussed within Section 4 Review of Safety, as applicable.

3 Integrated Review of Efficacy

Efficacy Summary

The Applicant has submitted a new efficacy supplement for ivacaftor, for the treatment of CF patients with an *R117H* mutation in the *CFTR* gene. The submission includes double-blinded, randomized, placebo-controlled data from Study 110, as well as

supportive data from an interim analysis from the open-label rollover study 112. Study 110 failed to meet its primary efficacy endpoint, the absolute change in percent predicted FEV1 from baseline through the 24-week treatment period. The change from baseline for patients who received placebo was 0.5 %, and 2.6%for those who received ivacaftor, resulting in a 2.1% increase in percent predicted FEV1 treatment effect (p=0.198). The treatment effect compares to a 10-13% increase in absolute percent predicted FEV1 compared to placebo which was observed in the *G551D* and related CF subpopulations for which ivacaftor is approved. Study 110 data was analyzed utilizing both the pre-specified secondary endpoints, as well as a series of subgroup analyses, to consider the heterogeneity in the phenotype of the *R117H* patient population. For the overall study population, patients from Study 110 who received ivacaftor demonstrated a significant decrease in sweat chloride (-24 mmol/L), as well as improvements in respiratory symptoms, measured as a mean change in CFQ-R respiratory domain (8.4 points). There was no significant difference in BMI or exacerbations between ivacaftor and placebo treatment groups for the overall population or any subpopulations. Other subpopulation analyses showed variable results.

Evaluations based on age showed a 5% improvement in FEV1, improvement in sweat chloride (decreased by 22mmol/L) and in CFQ-R respiratory domain (increased by 12.6 points) for patients >18 years, supporting a benefit of ivacaftor in this subset. However, data from patients 6-11 years of age showed a worsening of FEV1 (decreased by 6%) and symptom scores declined by 6.1 points (95% CI:-15.7, 3.4) for the ivacaftor group as compared to placebo. Sweat chloride decreased as expected, but why the children 6-11 years of age would worsen compared to placebo cannot be adequately explained.

Subpopulations based on poly-T tract showed a 5% improvement in FEV1 and improvement in CFQR-respiratory domain by 15.3 points in patients with confirmed *cis*-5T poly-T tract status and a 3% improvement in FEV1 in patients with confirmed + derived 5-T status combined. Patients with 7-T status had no improvement in FEV1, but the CFQ-R respiratory domain improved. Analyses based on lung function showed an improvement in FEV1 of 4.0% and 2.6% predicted in patients with baseline FEV1 of <70% and 70-90% predicted, respectively, and a decrease in FEV1 by 4.3% in patients with baseline FEV1 >90% predicted. Improvements in CFQR-respiratory domain of 11.4 and 8.8 in patients with baseline FEV1 of <70%, and 70-90% predicted, respectively, were also noted.

Overall, the multiple analyses conducted appear to show that at least some CF patients with a *R117H-CFTR* mutation demonstrate a benefit in response to treatment with ivacaftor.

3.1 Indication

The currently proposed indication is for the treatment of CF in patients age 6 years and older who have an *R117H* mutation in the *CFTR* gene.

3.2 Methods

This is a small efficacy supplement, which consists of a single randomized, controlled, 24-week trial (study 110), as well as open-label data through 12 weeks (interim analysis of Study 112), which, when taken in context with what is already known about ivacaftor in approved sub-populations of patients with CF, form the basis of an efficacy determination for patients with an *R117H* mutation in the *CFTR* gene. The overall design (mirroring that of Studies 102/103 from the *G551D* program) was discussed with the Applicant (as outlined in Section 1.6). The Division agreed that the choice of primary efficacy endpoint, general patient population, and study duration were reasonable. Statistical plans including two interim evaluations by a DMC (one early blinded analysis for safety, and a more formal interim analysis for efficacy and safety), were also discussed at a high level, and appeared reasonable.

Section 3 of this review (Efficacy) will primarily present the data from Study 110, the placebo-controlled trial. Data from Study 112, the open-label extension study (data from 65 patients from Study 110) will be included and discussed under Section 3.6 Supportive Analyses of this document.

Applicant's Pre-specified Analysis Methods

Study 110
The Applicant pre-specified that they would utilize a mixed-effects model for repeated measures (MMRM) for the primary efficacy analysis method, which assumes a stable treatment effect over time. The MMRM was used to analyze the effects of ivacaftor on FEV1, sweat chloride concentration, and CFQ-R respiratory domain at 24 weeks, with treatment group, categorical visit and treatment by visit interaction as fixed effects, with subject as random effect, and with adjustment for the continuous baseline values of age, percent predicted FEV1, and baseline of analyzed variable. The endpoint of change in BMI at 24 weeks was evaluated using a linear mixed model (LMM) with dependent variable weight, and treatment as a fixed effect, and with adjustment for covariates of baseline FEV1, age, and visit by treatment interaction. Multiple sensitivity analyses were proposed; final SAP submitted November 2013 included details for analysis.

Both the FDA and the Applicant have primarily used the Full Analysis Set (FAS) data for efficacy analysis, defined as all randomized patients who received at least one dose of study drug.

Study 112
The Applicant has submitted summary statistics for a subgroup of patients within Study 112 (those who enrolled in Study 110 and continued into 112) at an interim week 12 time point. Following the week 12 database lock for this subgroup, additional ad-hoc analyses were conducted. [Source: Module 2.7.3, SCE, section 1.3.9.2, page 24].

3.2.1 Subject Disposition

There were 108 subjects screened for participation in Study 110, 38 of who did not meet criteria for randomization. A total of 70 patients were randomized, 34 to ivacaftor, and 36 to placebo. One patient was randomized to placebo but never received a dose of study drug, leaving a total of 69 patients in the Full Analysis Set (FAS), defined as all patients randomized and having received at least one dose of study drug.

Subjects were randomized at 27 study sites within North America and Europe. Disposition is described in Table 4 below.

Table 4: Patient Disposition, Study 110

Disposition Category	Placebo n (%)	Ivacaftor n (%)	Total n (%)
All Screened	---	---	108
All Randomized[a]	36	34	70
Full Analysis Set (FAS)	35	34	69
Week 24 Completers[b]	31 (89%)	28 (82%)	59 (86%)
Did not Complete	4 (11%)	6 (18%)	10 (14%)
Reason:			
Early Study Termination	4 (11%)	4 (12%)	8 (12%)
Non-compliance		1 (3%)	1 (1%)
Pregnancy		1 (3%)	1 (1%)

a= one patient randomized to placebo, but did not receive any dose of study drug
b= 4 patients receiving placebo and 4 patients receiving ivacaftor, did not complete due to early study termination; an additional 2 patients in the ivacaftor group did not complete one non-compliance, one pregnancy)

[Source: Module 5.3.5.1 CSR for Study 110, Sections 10.1, 11.3.8.6]

The following Table 5 further characterizes those patients who did not complete to week 24 of the trial. Fifty-nine patients (86%) completed the 24-week treatment period.

Table 5: Disposition of Patients who did not Complete through Week 24, Study 110

Disposition Category	Placebo n (%)	Ivacaftor n (%)	Total n (%)
Full Analysis Set (FAS)	35	34	69
Week 24 Completers	31 (89%)	28 (82%)	59 (86%)
Did not Complete to Week 24	4 (11%)	6 (18%)	10 (14%)
Last Scheduled Visit Completed:			
Week 2[a]	1 (3%)	2 (6%)	3 (4%)
Week 4	1 (3%)	0	1 (2%)
Week 8	1 (3%)	2 (6%)	3 (4%)
Week 16[b]	1 (3%)	2 (6%)	3 (4%)

a= One of two subjects receiving ivacaftor was discontinued at week 2 due to non-compliance with ophthalmologic exam
b= one of the two subjects receiving ivacaftor discontinued at week 16 due to pregnancy
[Source: Module 5.3.5.1 CSR for Study 110, Sections 10.1, 11.3.8.6]

3.2.2 Demographics

Demographic data from the full analysis set for Study 110 are listed in Table 6, below. All patients were White, with only one patient reported of Hispanic ethnicity. Mean age was 31 years old, with 72% of patients 18 years or older. Average FEV1 was 73% of predicted, with 59% of patients demonstrating a baseline FEV1 over 70% predicted. Mean sweat chloride value was 70mmol/L, but there was significant variability around this parameter, with the lowest sweat chloride reported as 22mmol/L, and the highest value at 120mmol/L.

General demographics were similar between the two treatment groups, with noted small differences in FEV1 and BMI (higher in ivacaftor group), and baseline sweat chloride and *P. aeruginosa* infection rate (lower in ivacaftor group). Most of the patients were over age 18 (N=50). Only 2 patients aged 12-17 enrolled (one of whom received placebo, and the other discontinued early), and 17 pediatric patients aged 6-11 years were included. Fifty-three patients (77%) had the *R117H/F508del* genotype, and two patients (3%) were R117H/R117H homozygous. The remainder of patients (14) had another non-gating mutation, the majority of which were class I premature stop codon mutations (*W1282X, G542X, R553X, S489X*), or class II missense, splice, or insertion/deletions. The majority of patients were pancreatic sufficient with normal fecal elastase values (N=60, 87%), as evidenced by the low number of patients requiring pancreatic enzyme replacement (noted below). Baseline lung function observes 41% (n=28) of patients with FEV1<70%, 41% (n=28) with FEV1 70-90%, and 18% (n=13) with FEV1>90%. Twelve of the 13 patients with FEV1>90% predicted were in the 6-11 years subgroup.

Baseline concomitant medications were similar in both treatment groups, with less than 15% difference in use of standard CF therapies noted between groups, including

inhaled corticosteroids, inhaled and oral antibiotics, bronchodilators, mucolytics, and multivitamins.

There were 3 exceptions noted:

- “paracetamol” (acetaminophen) use, which noted 13 patients (37%) in the placebo group, versus 4 (12%) in the ivacaftor group,
- cetirizine, which noted 9 (26%) in the placebo group versus 3 (9%) in the ivacaftor group, and
- Pancreatic enzyme supplementation, which noted 7 (20%) in the placebo group versus 1 (3%) in the ivacaftor group.

None of these three treatments would be expected to significantly skew patient severity, with the possible exception of patients receiving pancreatic enzymes. In general, patients on pancreatic enzymes are pancreatic insufficient, and therefore may exhibit overall more severe phenotype than those not on enzymes; however, the small numbers in this study make in-depth evaluation and conclusions of questionable relevance.

Table 6: Patient Demographics and Baseline Characteristics, Study 110

Variable	Placebo N=35	Ivacaftor N=34	Total N=69
Sex, n (%)			
Male	15 (43%)	15 (44%)	30 (44%)
Female	20 (57%)	19 (56%)	39 (56%)
Age (years)			
Mean (SD)	32.7 (17)	29.2 (17)	31.0 (17)
Minimum, Maximum	6, 68	6, 55	6, 68
Age Group-years, n (%)			
6-11 years	8 (23%)	9 (27%)	17 (25%)
12- 17 years	1 (3%)	1 (3%)	2 (3%)
≥18 years	26 (74%)	24 (70%)	50 (72%)
Percent Predicted FEV1, Baseline			
Mean (SD)	70 (19)	76 (19)	73 (19)
Minimum, Maximum	37, 103	33, 106	33, 106
FEV1 Group, n (%)			
<70%	15 (43%)	13 (38%)	28 (41%)
70-90%	14 (40%)	14 (41%)	28 (41%)
>90%	6 (17%)	7 (21%)	13 (18%)
BMI (kg/m^2)			
Mean (SD)	23.1 (6.0)	24.5 (6.2)	23.8 (6.1)
Minimum, Maximum	13.6, 37.8	14.4, 42.9	13.6, 42.9
Pseudomonas aeruginosa Infxn, n (%)			
Yes	19 (54%)	15 (44%)	34 (49%)
No	16 (46%)	19 (56%)	35 (51%)
Pancreatic Sufficiency Status Fecal elastase-1, n (%)			
Insufficient (<200µg/g)	5 (14%)	2 (6%)	7 (10%)
Sufficient (≥200 µg/g)	28 (80%)	32 (94%)	60 (87%)
Missing value	2 (6%)	---	2 (3%)
Geographic Region, n (%)			
North America	30 (86%)	24 (71%)	54 (78%)
Europe	5 (14%)	10 (29%)	15 (22%)
Sweat Chloride, mmol/L[a]			
N	35	32	67
Mean (SD)	73.4 (20)	67.3 (19)	70.5 (19)
Minimum, Maximum	22.5, 108.8	23.3, 120	22.5, 120

a= Baseline sweat chloride was not collected for two patients at the time of randomization
[Source: Module 5.3.5.1 CSR for Study 110, Section 10.2.1.1, Table 10-2]

Reviewer's Comment:
Of note, 8 patients enrolled in this study had baseline sweat chloride values in the normal range (<40mmol/L). There were two patients who did not have baseline sweat values recorded (one missing baseline only, and the second having no sweat chloride

values for the study). In addition, there were eleven patients who had sweat chloride values at baseline which are considered in the "borderline" clinically diagnostic range, from 40 to 60mmol/L. Therefore, 8 of the total 69 patients (12%) had a sweat chloride value considered normal, and 21 of 69 (30%) had values normal, borderline, or missing. It is presumed that these patients were enrolled on the definition of "two alleles" (that cause CF) and clinical disease characteristics. See also 2.4.1 STUDY 110*, population, for discussion regarding enrollment, and Section* 3.5 Subpopulations *for subset analyses of efficacy data for these patients.*

Another important demographic variable to be considered within Study 110 is the Poly-T status of each allele. For the *R117H* mutation in particular, the Poly-T status can significantly contribute to a patient's phenotypic variability, with *cis*-5T demonstrating more significant disease, and *cis*-7Tor 9T to be associated with milder disease, if believed to be disease-causing[22]. While there are a few case reports of young patients[15, 16] and more reports of older patients[20, 21] who are *cis*-7T *R117H and* demonstrate symptoms of disease, the CFTR2 database characterizes an *R117H*-7T as "unlikely to act as a disease-causing mutation[17]." Evaluation of study 110 patients by their poly-T tract therefore becomes relevant, since the degree of improvement which might be seen with treatment is not uniform across the population, and values closer to the range of normal likely will not be able to improve as dramatically as in those with significantly abnormal parameters. Table 7 below provides baseline demographics by poly-T status, both confirmed (meaning that patients had allele-specific long-range PCR on the *R117H* mutation as part of the additional genetic testing within Study 110), and as confirmed + derived. The derived status was determined for 13 patients who did not have a confirmed poly-T status (did not contribute the optional blood sample), and who had either an *R117H* or *F508del* mutation on the second allele. Derived status was determined by attributing any 9T value to the second allele (since almost all *F508del* mutations are *cis*-9T, and a *cis*-9T is exceedingly rare for the *R117H* mutation[22]), therefore presuming that the remaining 5T or 7T was in the *cis*- configuration for the *R117H* allele. The two remaining patients carried non- *R117H* or *F508del* mutations in the second allele, and thus could not be derived by this method.

Table 7: Poly-T Tract Status, Study 110

R117H cis-Poly-T status, Confirmed[a], n (%)	Placebo N=29	Ivacaftor N=25	Total N=54
cis-5T	24 (83%)	14 (56%)	38 (70%)
cis-7T	5 (17%)	11 (44%)	16 (30%)
R117H cis-Poly-T status, Confirmed + Derived[b], n (%)	Placebo N=34	Ivacaftor N=33	Total N=67
cis-5T	27 (79%)	21 (64%)	48 (72%)
cis-7T	7 (21%)	12 (36%)	19 (28%)

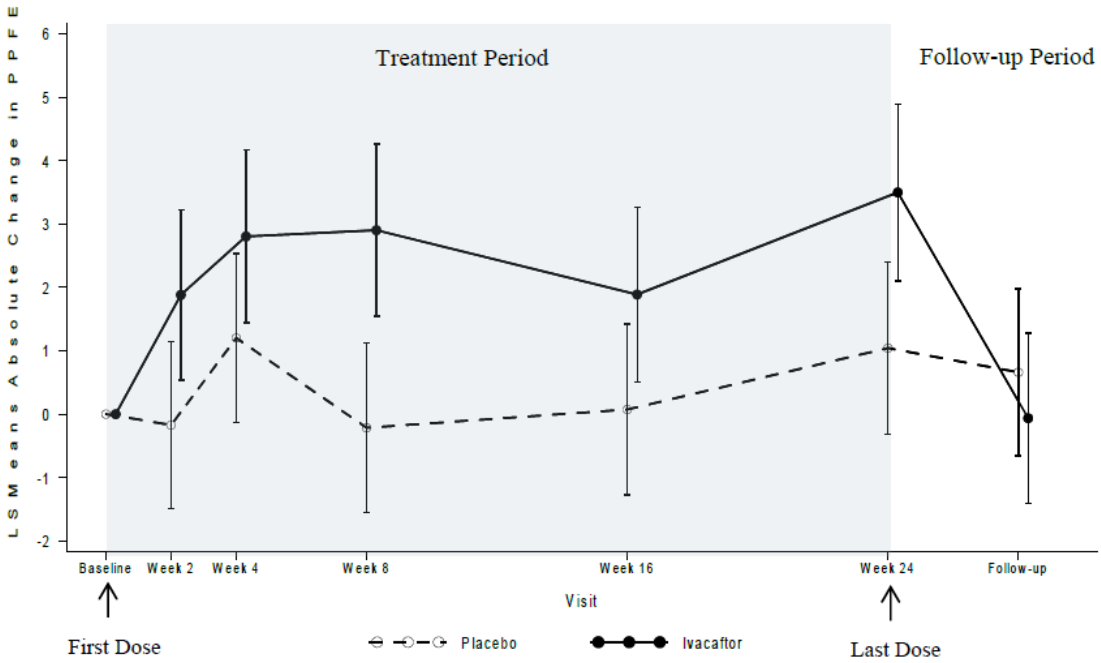
a= Confirmed includes only those patients who consented for additional genetic testing via allele-specific long-range PCR, which sequenced the *cis*-configuration for *R117H*
b= Derived status is determined for 13 patients who did not have a confirmed poly-T status, with a second *R117H* or *F508del* mutation on the second allele; any 9T value was attr buted to the second allele, presuming that the remaining 5T or 7T was in the *cis*- configuration for *R117H;* two patients carried different mutations, and could not be derived by this method
[Source: Module 5.3.5.1 CSR for Study 110, Section 10.2.1.1, Tables 10-2, 14.1.2.6ad, 14.1.2.7ad; SD-262, Response to FDA Request for Additional Information-R117H -dated 16 July 2014, Table 1]

3.3 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for Study 110 was the absolute change from baseline in percent predicted FEV1 through week 24; the study failed to meet its primary efficacy endpoint for the full analysis set. The treatment difference for ivacaftor versus placebo was 2.1% (95% CI: -1.1305, 5.3532); which was not statistically significant (p=0.1979). While not reaching statistical significance, the difference favored ivacaftor, with the mean absolute change from baseline in percent predicted FEV1 through Week 24 by MMRM for the FAS greater for the ivacaftor group (2.6%) than the placebo group (0.5%). Treatment effect favored ivacaftor at each time point (weeks 2, 4, 8, 16, and 24), as demonstrated in Figure 3: Primary Endpoint: Absolute Δ from Baseline FEV1 % Predicted, Study 110 FAS, below.

It is also important to note that at the end of study drug treatment, there is a drop in FEV1 for patients who received ivacaftor by the washout Follow-up Visit; this will be addressed in more detail in Section 3.6 Supportive Analyses, later in this review.

Figure 3: Primary Endpoint: Absolute Δ from Baseline FEV1 % Predicted, Study 110 FAS



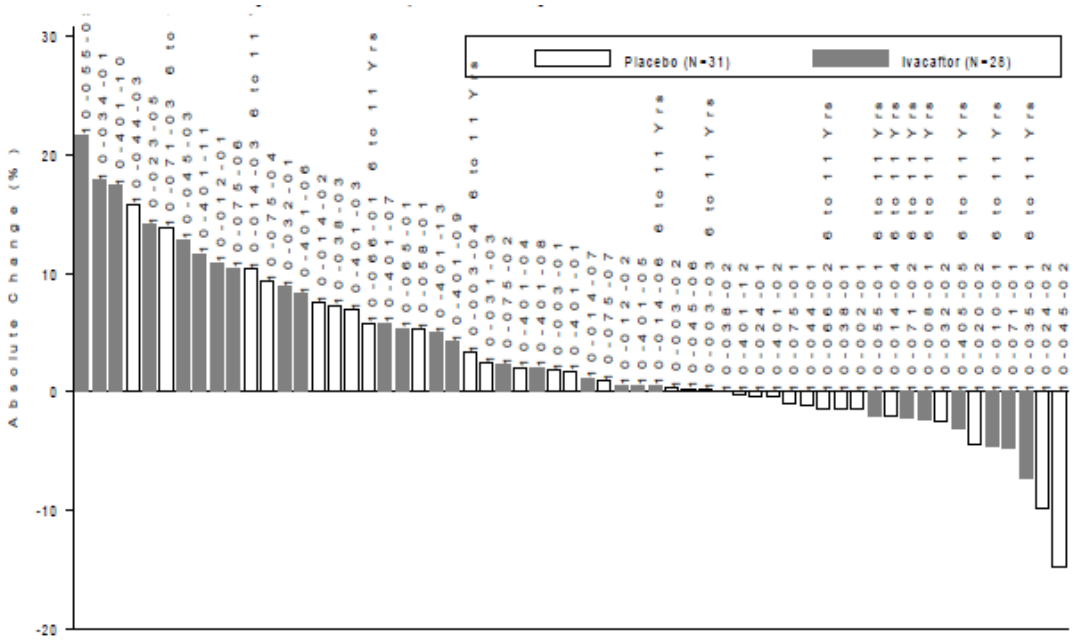
[Source: Module 5.3.5.1 CSR for Study 110, Section 11.3.2, Figure 11-1]

Multiple sensitivity analyses were conducted by the Applicant, and were consistent with the primary endpoint, in that no statistically-significant treatment benefit was noted, but all showed a numerically positive treatment difference for ivacaftor compared to placebo [data not shown; Source: Study 110 CSR, Table 11-4, page 130].

The Applicant also provided a waterfall plot by which to view the trend of effect for all patients, shown below in Figure 4. It was noted that of the 28 patients in the ivacaftor group who completed 24 weeks of treatment, 20 improved, 1 had no change, and 7 declined, and that 6 of the 7 who declined were in the pediatric group. These observations led the Applicant to conduct a number of evaluations to look at data from subgroups, which resulted in the Applicant initially limiting the indication to the adult CF population with an *R117H* mutation (see Section 3.5 Subpopulations, of this review).

In addition, a responder analysis of the primary endpoint for the full analysis set was assessed, and also demonstrated no statistically-significant differences, but again a trend toward benefit with ivacaftor was noted. The Applicant's table is included in Table 8, below.

Figure 4: Waterfall Plot, Absolute Δ in Baseline % Predicted FEV1, Study 110, FAS



[Source Module 5.3.5.1, CSR 110, Figure 11-2, p 129]

Table 8: Responder Analysis of Absolute Δ from Baseline FEV1 % Predicted, Study 110 FAS

Category	Placebo N = 35 n (%)	Ivacaftor N = 34 n (%)	*P* value
≥3.5%	8 (22.9)	13 (38.2)	0.1975
<3.5%	27 (77.1)	21 (61.8)	
≥5%	7 (20.0)	13 (38.2)	0.1165
<5%	28 (80.0)	21 (61.8)	
≥7.5%	4 (11.4)	8 (23.5)	0.2182
<7.5%	31 (88.6)	26 (76.5)	
≥10%	2 (5.7)	5 (14.7)	0.2595
<10%	33 (94.3)	29 (85.3)	

Sources: Table 14.2.1.1.7 and Table 14.2.1.1.7.1ad through Table 14.2.1.1.7.4ad.
Note: Absolute change through Week 24 is the average change from baseline over 24 weeks for percent predicted FEV_1.

[Source Module 5.3.5.1, CSR 110, Table 11-5, p 131]

Because the *R117H* mutation is a different sub-population than that for which ivacaftor was originally developed, it is useful to describe the treatment effect of ivacaftor in Study 110 to the effects noted within the entire ivacaftor development program. Based on the molecular differences between types of mutations, and ivacaftor's effects on the CFTR protein, it was not clear how much effect one might expect ivacaftor to produce in this distinct subgroup of CF patients.

Patients with an *R117H* mutation exhibit much more heterogeneity in their CF phenotype than patients with *G551D* or *F508del*, in part due to the poly-T region of intron 8. Patients with this mutation tend to have lower sweat chloride values, less lung disease, and most are pancreatic sufficient, although disease presentation may vary widely, even within the same subsets. For these reasons, early meetings with the Applicant discussing the design of Study 110 stressed that the treatment effect of ivacaftor was uncertain, and convincing clinical data would be needed to be able to make the determination that this small molecule could affect mutations in a different Class than the one for which it was designed.

Because patients with the *R117H* mutation may not have as severe a disease phenotype as patients with the *G551D* or other related mutations, it is not unreasonable to consider that 24 weeks may be too short of a timeframe for these *R117H* patients to demonstrate a decline in lung function, such that a change would be harder to measure. In addition, since ivacaftor is able to increase channel-open time even in wild type (normal) CFTR protein, we would expect that some beneficial treatment effect of ivacaftor might be identified, if not in lung function. For these reasons, we will also consider secondary efficacy endpoints, as well as subgroup analyses, in the subsequent sections.

3.4 Analysis of Secondary Endpoints

It is useful to examine the efficacy of ivacaftor in the context of other studies within the development program. The following table is a graphic representation of primary and key secondary endpoints, which will be discussed in more detail in each sub-section, below.

Table 9: Effect of Ivacaftor Across Studies Within the Development Program

			Treatment Effect Across Study Period				
Study # population	**Study duration**	**N**	**Sweat Chloride**	**FEV1 % Predicted**	**CFQR-resp**	**Weight/ BMI**	**CF Exac.**
102 *G551D* ≥12yo	24 wk[a]	213	**-48** (-51, -45)	**10.6%** (8.6, 12.6)	**8.1** (4.7, 11.4)	**+2.8kg** (1.8, 3.7)	**RR=0.4**[b] (0.23, 0.71)
103 *G551D* 6-11yo	24 wk[a]	52	**-54** (-62, -47)	**12.5%** (6.6, 18.3)	**6.1** (-1.4, 13.5)	**+1.9kg** (0.9, 2.9)	NA
111 Similar fxn ≥6yo	8wk	39	**-49** (-57, -41)	**13.8%** (9.9, 17.6)	**12.8** (6.7, 18.9)	**0.66 kg/m^2** (0.34, 1.32)	NA
104 *F508del* ≥12yo	16 wk	112	**-2.9** (-5.6, -0.2)	**1.7%** (-0.6, 4.1)	**1.3** (-2.9, 5.6)	**-0.16kg** (-1.1, -0.7)	NA
110 *R117H* ≥6yo	24wk	69	**-24** (-28, -19.9)	**2.1%** (-1.1, 5.3)	**8.4** (2.2, 14.6)	**0.26 kg/m^2** (-1.6, 2.1)	**HR=0.93**[c]

a= Study primary efficacy was to week 24, but blinded data out to 48 weeks supported efficacy
b= relative risk of exacerbation
c= time-to-first exacerbation, hazard ratio
[Sources: Ivacaftor patient labeling; NDA 203-188 Primary clinical review dated Jan 17, 2012 and Primary Statistical Review Jan 13 2012, Table 16; NDA 203-188 supplement-14, CSR Study 110; SD-258 additional data submission 07/03/2014]

3.4.1 Change in Sweat Chloride

Change in sweat chloride is an important pharmacodynamic parameter which has been used within the ivacaftor program, to support an effect of ivacaftor on the CFTR chloride channel. It is in this context that we examine the sweat chloride changes in *R117H* patients.

In Study 110, ivacaftor was able to demonstrate a pharmacodynamic effect on sweat chloride values versus placebo. The mean treatment effect of ivacaftor was -24mmol/L. The average sweat chloride at baseline was 67mmol/L for the ivacaftor group, and 73mmol/L for placebo, with a -2mmol/L difference at 24 weeks in placebo, but a -26.3 mmol/L decline in ivacaftor-treated patients at week 24 [Source Module 5.3.5.1, CSR 110, Table 11-6, p 132]. This change was noted at week 2 and persisted throughout treatment. While the overall treatment effect was roughly half of that in the original program, taking the lower baseline sweat chloride values into consideration, it appears that there is a pharmacodynamic effect of ivacaftor measurable in this *R117H* population, which provides a relative 40% decrease in sweat chloride values for the ivacaftor treatment group.

In the initial G551D program, mean sweat chloride values at baseline were 100 and 104 mmol/L in each of the two trials, and declined by -48 and -54mmol/L, respectively, at week 24, representing a 50% relative decrease in sweat chloride. The sweat chloride decrease was noted at the first study time point (day 15), and persisted through 48 weeks of blinded treatment. While individual patient sweat chloride levels did not correlate with individual lung function values, the mean overall decline in sweat chloride for the group was pronounced and persistent over time, indicating a pharmacodynamic effect in chloride transport. For patients with mutations functionally similar to *G551D* (Study 111), the average sweat chloride at baseline was also around 100mmol/L, and decreased by 49mmol/L for the group, at week 8, demonstrating a similar treatment effect to the *G551D* group. For the *F508del*-homozygous patients evaluated in Study 104, the baseline sweat chloride values were also around 100mmol/L, but no treatment effect was seen, with a -3mmol/L difference measured at week 16. This was expected based on the mechanism of action, in that, with the *F508del*-mutation, little to no CFTR is found at the apical cell membrane.

3.4.2 Change in BMI

For patients in Study 110, the improvement from baseline in BMI did not change significantly over the 24 week study period, as shown below. The mean rate of change from baseline in BMI at Week 24 notes a treatment difference of 0.26 kg/m^2 (95% CI: -1.57, 2.10) which favored ivacaftor, but was not statistically significant (p =0.7780). However, since the majority of patients enrolled (87%, or 60 of 69 patients) were considered pancreatic sufficient based on their fecal elastase-1 values at baseline, it is not clear how much of a change would therefore be expected clinically.

Table 10: Rate of Δ from Baseline in BMI, Study 110, FAS

Visit or Time Period	Treatment Group	Sample Statistics		Rate of Change in Treatment Period[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	35	23.066	--	--	--	--
	Ivacaftor	34	24.480	--	--		
Week 24	Placebo	31	23.735	35	0.2284	0.2626 (-1.5698, 2.0950)	0.7780
	Ivacaftor	28	24.542	34	0.4910		

Source: Table 14.2.4.2.5.
Note: Sample statistics are unadjusted results.
[a] Estimated change from baseline per 168 days was obtained from a linear mixed model, with BMI as the dependent variable; with treatment as a fixed effect; with intercept and visit (days on study, including all visits through Week 24) as random effects; and with adjustment for baseline percent predicted FEV_1, age, and visit by treatment interaction included as covariates in the model.
[b] *P* value for the treatment effect is from the slope of BMI (kg/m^2) versus time (days).

[Source Module 5.3.5.1, CSR 110, Table 11-9, p 135]

BMI-for-age z-scores were also evaluated for 22 patients who were 20 years of age or younger; again, while rate of change from baseline was greater for ivacaftor than

placebo groups, the difference of 0.099 points did not meet the level that would have been considered statistically significant.

Because patients with the *G551D* mutation (and functionally-related mutations) in general exhibit pancreatic insufficiency as part of their CF disease, demonstration of weight gain was considered a relevant and clinically meaningful efficacy endpoint. In the ivacaftor program to date, the treatment differences between ivacaftor and placebo groups were significant in all populations with approved indications (see attached prescribing information for ivacaftor).

3.4.3 Time to first Exacerbation

The time-to-first pulmonary exacerbation by treatment group was assessed as a secondary efficacy endpoint for Study 110; the calculated hazard ratio of 0.93 numerically favored ivacaftor, but did not meet the level at which it would have been considered statistically significant (p=0.8556).

The study in patients 12 years and older with a *G551D* mutation in *CFTR* assessed the occurrence of exacerbations as a relative risk between groups. In that study, ivacaftor demonstrated a relative risk of 0.4 at week 24, and 0.46 at week 48 as compared to the placebo group. (The study in younger patients did not prioritize exacerbation as a key secondary endpoint, since younger, healthier patients are less likely to demonstrate exacerbations as compared to an older, sicker population). Study 111 in patients with functionally similar mutations, was an 8 week crossover trial, which was too short in duration to adequately assess exacerbation risk.

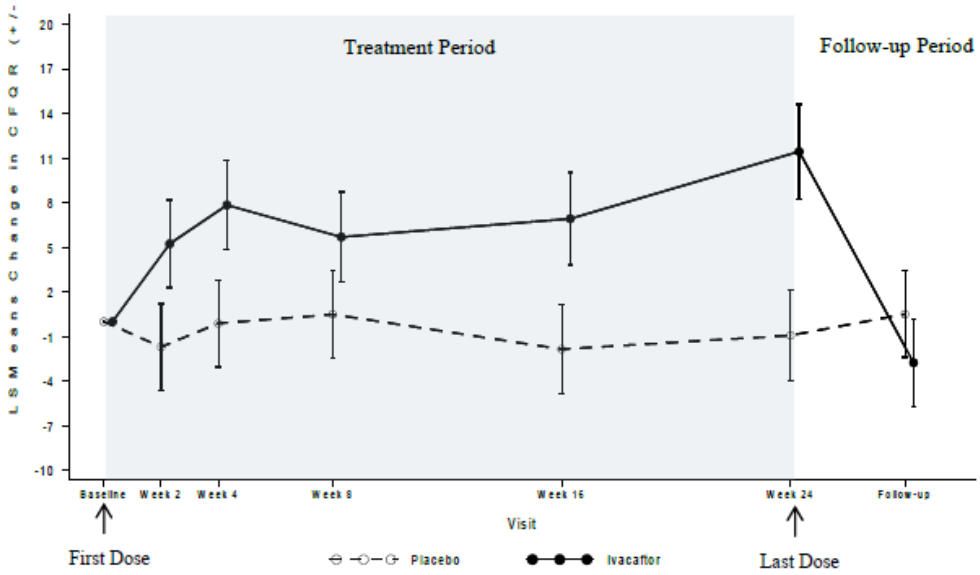
3.4.4 Change in CFQ-R Respiratory Domain

The CFQ-R respiratory domain score was evaluated within Study 110. The minimum clinically important difference (MCID) for this patient-reported symptom scoring system is a difference of 4 points for stable patients[18]. The mean absolute change from baseline in the pooled CFQ-R respiratory domain score through Week 24 by MMRM was greater for the ivacaftor group (7.6 points) than the placebo group (-0.8 points). The overall treatment difference for ivacaftor versus placebo was 8.4 points (95% CI: 2.17, 14.61). This analysis favored ivacaftor, with differences of 5 to 12 points between groups at each time point.

However, it is important to note that the lower bound of the confidence interval does not meet the MCID. Also, the interpretability of the MCID in this *R117H* population is uncertain, given that the MCID value of 4 points was calculated in a program for inhaled antibiotics, in patients chronically infected with *Pseudomonas aeruginosa*; in this Study 110 population, only 49% of patients were chronically infected with *Pseudomonas* [Source Module 5.3.5.1, CSR 110, Table 10-2, p 113].

Note also at the end of study drug treatment (week 24), there is a drop in scores for patients who received ivacaftor by the end of washout Follow-up Visit; this will be addressed in more detail in Section 3.6 Supportive Analyses, later in this review.

Figure 5: Mean Absolute Δ from Baseline in CFQ-R Respiratory Domain Scores



[Source Module 5.3.5.1, CSR 110, Figure 11-7, p 143]

Changes in CFQ-R respiratory domain were evaluated within the original *G551D* program, as well as in Study 111 for the functionally-related gating mutations. In the original program, it was noted that the CFQ-R scores did not directly correlate with FEV1, indicating that this patient reported outcome measure was quantifying a somewhat different parameter of how patients with CF feel and function. Patients ≥12 years old with a *G551D* mutation noted an improvement of 8.1 points (95%CI: 4.7, 11.4) at week 24, and 8.6 points ((95%CI: 5.3, 11.9) at week 48. The younger patients also noted numerical improvements of 6.1 and 5.1 points at weeks 24 and 48, respectively, but these did not achieve statistical significance. For patients in Study 111, there was a treatment difference of 12.8 points (95%CI: 6.7, 18.9) at week 8, which was highly significant.

3.5 Subpopulations

Due to the variability within this small group of patients, it was felt that exploration of groupings of this heterogeneous population might be useful. Below is a table of patient demographics within sub-populations; each sub-population will be explored further in the following sections below.

Table 11: Demographics by Various Sub-populations, Study 110

	Placebo N=35, (n%)	Ivacaftor N=34, (n%)	Total N=69, (n%)
Age Category			
6 to 11	8 (23)	9 (27)	17 (25)
12-17	1 (3)	1 (3)	2 (3)
≥18	26 (74)	24 (71)	50 (72)
% predicted FEV1, All Patients			
<70%	15 (43)	13 (38)	28 (41)
70 to ≤90%	14 (40)	14 (41)	28 (41)
>90%	6 (17)	7 (21)	13 (18)
% predicted FEV1, 6 to 11yo[a]			
<70%	--	--	--
70 to ≤90%	2 (25)	3 (33)	5 (30)
>90%	6 (75)	6 (67)	12 (70)
% predicted FEV1, ≥18yo[b]			
<70%	15 (58)	13 (54)	28 (56)
70 to ≤90%	11 (42)	10 (42)	21 (42)
>90%	---	1 (4)	1 (2)
Poly-T Status, confirmed (N=54)			
5T	24	14	38
7T	5	11	16
Poly-T, Confirm+Derived (N=67)			
5T	27	21	48
7T	7	12	19
Age ≥18yo and Poly-T			
>18, 5T	21	17	38 (76)
>18, 7T	4	6	10 (20)
>18, unknown	***	***	2 (4)
Age 6-11yo and Poly-T			
6-11, 5T	5	4	9 (53)
6-11, 7T	3	5	8 (47)

a= Inclusion for children 6-11yo allowed an FEV1 as high as 105% at baseline
b= Inclusion for children >12yo and adults allowed an FEV1 as high as 90% at baseline
[Source: Module 5.3.5.1, CSR 110, Tables 10-2, 10-3, 10-4; Module 2.5, Clin overview Section 4.2; SD-262 supplemental data tables; SD-258, supplemental data tables]

3.5.1 Subgroups by Age

Of the 50 adult patients in the study, 24 received ivacaftor and 26 received placebo. Demographics by age note a mean % predicted FEV1 of 64.5%; only one patient had a baseline FEV1 over 90% predicted. The average sweat chloride value was 72mmol/L, with a minimum of 23 and max of 120mmol/L, demonstrating a wide variation of disease, even within this subgroup. 84% were pancreatic sufficient, and 64% were chronically infected with *Pseudomonas aeruginosa*. Of the 50 adults, poly-T status was

known or derived for 48. There were 29 adult patients with confirmed *cis*-5T, and 38 when 9 patients were added due to a derived *cis*-5T being assigned. There were 8 adults with *cis*-7T, and an additional 2 in whom *cis*-7T was derived, so 79% of adults ≥18 years were confirmed or derived to have the more severe *cis*-5T. [Source: SD-258 (7/03/2014) Module 5.3.5.1, Table 2, page 3, and SD-262 (7/16/2014), Module 1.11.3, Table 2, p 6]

Results for adults aged ≥18 years are shown in Table 12 below. In general, the adult population demonstrated a 5% improvement in FEV1 across visits.

Table 12: Absolute Δ from Baseline in % Predicted FEV1, >18yo

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value[b]
Baseline	Placebo	26	62.2149	--	--	--	--
	Ivacaftor	24	67.0287	--	--		
Week 2	Placebo	26	61.2118	26	-1.0018	5.0219 (0.7767, 9.2671)	0.0211
	Ivacaftor	24	71.0501	24	4.0201		
Week 4	Placebo	25	62.3104	25	0.1948	4.4098 (0.1469, 8.6727)	0.0428
	Ivacaftor	24	71.6345	24	4.6046		
Week 8	Placebo	25	60.9803	25	-1.1356	5.0418 (0.7789, 9.3048)	0.0211
	Ivacaftor	24	70.9361	24	3.9063		
Week 16	Placebo	24	62.7592	24	-0.6325	4.5128 (0.2062, 8.8193)	0.0402
	Ivacaftor	22	71.3331	22	3.8802		
Week 24	Placebo	23	63.4883	23	0.2918	5.8371 (1.4985, 10.1758)	0.0090
	Ivacaftor	21	73.3514	21	6.1289		

Source: Table 14.2.1.2.2.2ad.
Note: Sample statistics are unadjusted results. Difference is Ivacaftor – Placebo. A positive difference favors ivacaftor.
[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment, categorical visit (Weeks 2, 4, 8, 16, and 24), and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of percent predicted FEV_1 using compound symmetry covariance matrix.
[b] *P* values at individual visits are from linear contrasts between the 2 treatments effects at the given visit.

[Source Module 5.3.5.1, CSR 110, Figure 11-30, p 160]

Likewise, the changes in sweat chloride (decreased by 22mmol/L) and in CFQ-R respiratory domain (increased by 12.6 points), also support a benefit of ivacaftor in this subset. Small numerical changes in BMI were noted favoring ivacaftor (0.3 kg/m^2), with limited clinical relevance. The time-to-exacerbation data were similar to that of the FAS, and not generally supportive. Data for absolute percent predicted FEV1, sweat chloride, and CFQ-R respiratory domain results are listed in Table 13, below, in comparison to the other age groups.

Table 13: Efficacy Endpoints by Age Subgroups, Study 110

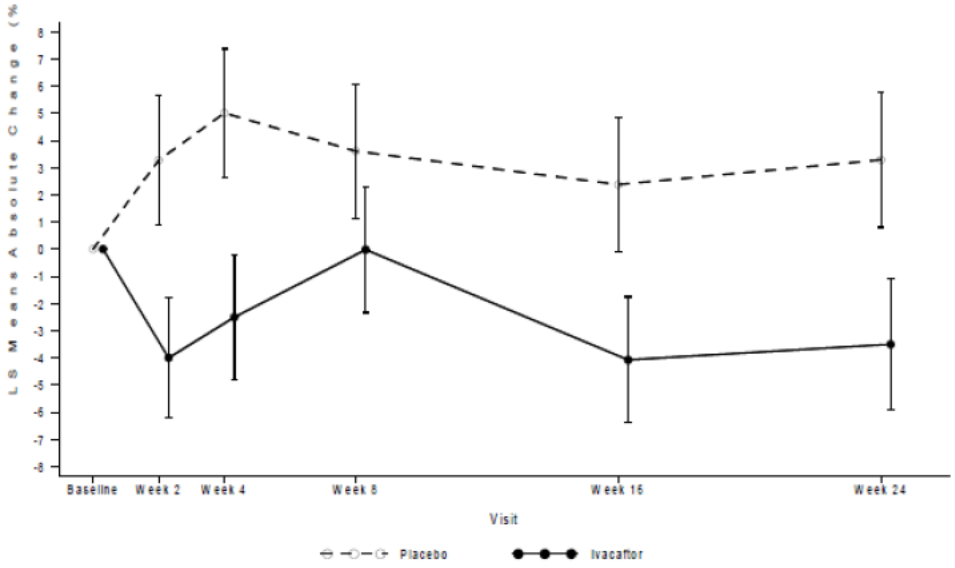
		Change through Week 24								
		% Predicted FEV1 (%)			Sweat Chloride (mmol/L)			CFQ-R respiratory (points)		
Age	Study Drug	n	Mean[a] abs. Δ	Difference (95%CI)	n	Mean[a] abs. Δ	Difference (95%CI)	n	Mean[a] abs. Δ	Difference (95%CI)
6 to 11	Placebo	7	3.3	-6.8	8	1.0	-27.6	7	-1.6	-6.1
	Ivacaftor	7	-3.5	(-13.9, 0.3)	8	-26.6	(-37.2, -18.1)	8	-7.7	(-15.7, 3.4)
12-17[b]	Placebo	1	---	---		---	---		---	---
	Ivacaftor	0								
≥18	Placebo	26	-0.5	5.0	26	-4.0	-21.9	26	-0.5	12.6
	Ivacaftor	24	4.5	(1.2, 8.8)	23	-25.9	(-26.5, -17.3)	24	12.2	(5.0, 20.3)

a= Mean absolute change from baseline to study end, by treatment group
b= one placebo patient [10-014-02] completed through week 24; one ivacaftor patient [10-033-02] was discontinued at Week 2 for non-compliance with ophthalmologic exam

Source: Module 5.3.5.1, CSR for Study 110, Tables 11-29, 11-33, 11-36, 11-42, 11-45, 11-49, section 11.3.6.2.

These adult results are markedly different from the mean data in children with an *R117H* mutation, in which a negative treatment effect for ivacaftor compared to placebo was observed (Figure 6, below).

Figure 6: Change from Baseline in % Predicted FEV1, 6-11yo



[Source Module 5.3.5.1, CSR 110, Figure 11-17, p 178]

This difference cannot clearly be explained based on the proposed mechanism of action, in that, children with dysfunctional CFTR chloride channels should benefit as well as adults. The Sponsor addresses this by stating that the children were relatively healthy, with mean FEV1 of 96%, so changes in FEV1 were minimal. This rationale might explain why children might not have demonstrated an improvement, but does not

explain why there was a negative effect. Within the original NDA, Study 103 in *G551D* patients noted 22% of the 6-11yo children had an FEV1 ≥90% predicted at baseline, and were still able to demonstrate a 7% clinically-meaningful improvement in absolute FEV1 [see Table 14 below]. In this subset of children in Study 110, 12 of the 17 patients (70%) have an FEV1 at baseline greater than 90% predicted, so there is less room for improvement. In addition, more pediatric patients in Study 110 were cis-7T, as compared to those over 18, again noting a "less sick" pediatric population. These reasons might support why patients would not improve, but do not necessarily explain a decrease compared to placebo. The Applicant notes that one pediatric patient on ivacaftor had an exacerbation at week 16, which could have driven down the mean FEV1 for the MMRM analysis, but in reviewing the waterfall plot in Figure 4, of the 7 ivacaftor-treated patients who had a negative treatment effect, 6 of the 7 were pediatric patients. Therefore the one patient alone might have contributed to the magnitude of the negative effect, but was not solely responsible for the negative effect seen. However, as FDA statisticians note, finding a negative effect in the small pediatric group could be attributable to chance [See Primary Biostatistical Review].

The symptom score for patients receiving ivacaftor also worsened in relation to placebo (see Table 13 above), but values for sweat chloride demonstrate a decrease which suggest a positive pharmacodynamic effect.

Table 14: Δ in % Predicted FEV1, by Pediatric Sub-group

Study #	Allele	N	% pts with FEV1 >90%	Treatment effect
103	*G551D*	52	22% (n=11)	Sub-group: 7% improvement
110	*R117H*	17	71% (n=12)	Overall group: 6% decline
Source: NDA 203-188 primary clinical Review, Table 9, page 50 and Suppleement-14, Module 2.5, Clin Overview, p 77-81				

3.5.2 Subgroups by Poly-T Status

Another way to examine this data is by poly-T status. As previously described, having a *cis*-5T configuration modifying the *R117H* mutation, in general, conveys more severe disease phenotype, and somewhat less variability. The data based on poly-T status can be further divided for Study 110 into two groups; those with a confirmed poly-T for the cis- confirmation (N=54), meaning that patients had allele-specific long-range PCR on the *R117H* mutation as part of the additional genetic testing within Study 110, and as confirmed + derived. The derived status was determined for 13 patients who did not have a confirmed poly-T status (did not contribute the optional blood sample), and who had either an *R117H* or *F508del* mutation on the second allele. Derived status was determined by attributing any 9T value to the second allele (since almost all *F508del* mutations are *cis*-9T), therefore presuming that the remaining 5T or 7T was in the *cis*-

configuration for the *R117H* allele. The two remaining patients carried non- *R117H* or *F508del* mutations in the second allele, and thus could not be derived by this method. Data for the primary efficacy endpoint for these subgroupings is shown below; tables are identified as "confirmed" or "confirmed + derived," as applicable.

Reviewer's Comment:
While the Applicant's method of deriving poly-T status appears reasonable (given that the vast majority of F508del-CFTR mutations are cis-9T), it is not clear why they did not utilize historical patient data since obtaining allele-specific long-range PCR is the clinical standard of care for patients testing positive for an R117H mutation.

Table 15: Absolute Δ from Baseline in % Pred FEV1, Confirmed Poly-T (n=54)

Poly T	Treatment	N	LS mean (SE)	Difference (95% CI)
5T	Ivacaftor	14	6.02 (1.57)	5.295 (1.27, 9.32)
5T	Placebo	24	0.73 (1.20)	
7T	Ivacaftor	11	-0.72 (2.09)	0.200 (-8.14, 8.53)
7T	Placebo	5	-0.92 (3.09)	

Source: Modified from Sponsor's Table 2, page 6, Submitted in Response to FDA request, package dated 7/16/2014

Table 16:Abs. Δ from Baseline in % Pred FEV1, Confirmed + Derived Poly-T (n=67)

Poly T	Treatment	N	LS mean (SE)	Difference (95% CI)
5T	Ivacaftor	21	5.39 (1.65)	3.191 (-0.48, 6.87)
5T	Placebo	27	1.00 (1.44)	
7T	Ivacaftor	12	-1.23 (2.37)	-1.464 (-8.69, 5.76)
7T	Placebo	7	2.00 (3.03)	

Source: Modified from Sponsor's Table 2, page 3, Submitted in Response to FDA request, package dated 7/03/2014

In both cases, the data from the poly -5T patients demonstrates a larger improvement than the 7T groups; however, looking at individual patient data, there is variability even in such smaller sub-divisions of subgroups. While most patients with cis-7T had a

higher baseline FEV1, there are patients who demonstrate impaired lung function at baseline as well, for example:

- Patient 10-012-03, 7T/ 9T, baseline sweat chloride 23mmol/L, with baseline FEV1 of 67% predicted; FEV1 declines to 44% predicted by week 8 with an exacerbation (IVA); this patient demonstrates significant baseline disease, and a clinically-meaningful exacerbation, despite 7T/9T status; [data only available to week 8 due to early study termination]
- Patient 10-032-01, 7T/ 9T, baseline sweat chloride 35mmol/L, with baseline FEV1 of 32% predicted, improves to FEV1 42% predicted (IVA), (10% improvement in absolute % predicted FEV1/ relative 30% improvement)

Table 17 below also provides the data for primary and important secondary endpoints, divided utilizing the "Confirmed plus Derived" poly-T status, in order to better evaluate treatment effect across endpoints. Differences in sweat chloride and symptom score for the *cis*-5T group are supportive, whereas for the *cis*-7T, although sweat chloride demonstrates a decrease, FEV1 is negative, and symptom score fails to meet the minimum difference of 4 points.

Table 17: Efficacy Endpoints by Poly-T Tract Subgroup, Study 110

		Change through Week 24					
		% Predicted FEV1 (%)		Sweat Chloride (mmol/L)		CFQ-R respiratory (points)	
Poly-T Status[a]	Study Drug	n	Difference (95%CI)	n	Difference (95%CI)	n	Difference (95%CI)
***cis*-5T**	Placebo Ivacaftor	21 27	3.2 (-0.5, 6.9)	20 27	-25.1 (-30.1, -20.0)	20 27	9.6 (2.6, 16.7)
***cis*-7T**	Placebo Ivacaftor	12 7	-1.5 (-8.7, 5.8)	11 7	-20.6 (-28.1, -13.1)	12 6	2.3 (-14.4, 19.1)

a= Confirmed +Derived poly-T tract data, n=67

Source: Module 5.3.5.1, CSR for Study 110, Tables 14.2.1.2.2.8.1ad, 14.2.1.2.2.8.2ad, 14.2.2.2.2.6.1ad, 14.2.2.2.2.6.2ad, 14.2.3.2.2.5.1ad, 14.2.3.2.2.5.2ad; NDA submission SD-258 Supplement, Tables 2, 3, 4..

However, patient 10-075-06 had *cis*-7T, with baseline FEV1 of 86% predicted, but improved to 97% predicted by study end after treatment with ivacaftor. Therefore, it is possible that any potential limitations to the indication based on a poly-5T status could exclude patients with a *cis*-7T who could potentially benefit from ivacaftor.

3.5.3 Subgroups by Lung Function

Examination of the results by Baseline FEV1 is an alternate way to evaluate the potential for benefit of ivacaftor in this *R117H* patient population, given the variability of phenotype across this heterogeneous sub-group. The greatest treatment differences

were noted in the subgroup of patients with the lowest lung function, as noted in Table 18, below.

Table 18: Efficacy Endpoints by % Predicted FEV1 at Baseline, Study 110 FAS

		% Predicted FEV1 (%)			Sweat Chloride (mmol/L)			CFQ-R respiratory (points)		
Baseline FEV1 value	Study Drug	n	Mean[a] abs. Δ	Difference (95%CI)	n	Mean[a] abs. Δ	Difference (95%CI)	n	Mean[a] abs. Δ	Difference (95%CI)
<70%	Placebo	15	0.5	4.0	15	-3.8	-25.5	15	3.0	11.4
	Ivacaftor	13	4.5	(-2.1, 10.2)	12	-29.3	(-31.8, -19.3)	13	14.4	(1.2, 21.6)
≥70 to ≤90%	Placebo	14	0.2	2.6	14	-3.1	-20.0	13	-3.6	8.8
	Ivacaftor	14	2.8	(-2.3, 7.5)	14	-23.0	(-26.9, -13.0)	14	5.2	(-2.6, 20.2)
>90%	Placebo	6	2.2	-4.3	6	1.0	-26.8	6	-2.5	-0.7
	Ivacaftor	7	-2.1	(-9.9, 1.3)	6	-25.9	(-39.5, -14.1)	6	-3.2	(-10.4, 9.0)

a= Mean absolute change from baseline to study end, by treatment group

Source: Module 5.3.5.1, CSR for Study 110, Table 11-71, and Tables 14.2.1.2.4, 14.2.2.2.3, and 14.2.3.2.3.

Limitation of the treatment population by baseline lung function could be problematic, for three major reasons. The first is that lung function will decrease when patients experience CF pulmonary exacerbations, so determining a "start value" for ivacaftor using lung function would be complex. A second issue is that the lung function decline in CF disease is characteristically a chronic decline over time, and it is unknown if ivacaftor could prevent or delay a progressive worsening in lung function over time. The current approved indication suggests this is the case, and it may be that patients with normal lung function at baseline could still benefit from treatment, even if pulmonary function did not improve. A third reason is that ivacaftor demonstrated efficacy across endpoints in the original program, such that utilizing a lung function cutoff could limit access to patients who might have more severe GI disease, for example.

3.5.4 Subgroup of Patients with Normal Sweat Chloride at Baseline

As discussed in the general demographics section, there were a number of patients within this small study who were randomized to study treatment, but had sweat chloride values in the normal range, meeting inclusion criteria by having two CF mutations, and "evidence of sinopulmonary disease." Within the total FAS population, 8 subjects (12%) had a baseline sweat chloride value <40mmol/L, which is considered normal. All were noted as *cis*-7T (6 were confirmed, and 2 were derived). Of this same group, 4 subjects also had a baseline FEV1 over 80% of predicted, but the range of baseline FEV1 was as low as 32% to as high as 105% of predicted. Primary efficacy results for the group, minus these 8 patients, are provided in the table below.

Table 19: Abs. Δ from Baseline in % Predicted FEV1, Sweat Chloride >40mmol/L

Population	Placebo		Ivacaftor		Difference vs Placebo (95% CI)	P value
	n	LS Mean	n	LS Mean		
Full Analysis Set	35	0.4611	34	2.5724	2.1114 (-1.1305, 5.3532)	0.1979
Sweat Chloride Set*	33	0.7853	28	3.6622	2.8769 (-0.4192, 6.1730)	0.0859

*Excluding 8 subjects enrolled who had a NORMAL Sweat chloride (<40mmol/L), they are 10-003-02, 10-012-03, 10-023-01, 10-032-01, 10-033-04, 10-035-01, 10-038-02 and 10-055-01

The above estimates were obtained from a mixed effects model for repeated measures (MMRM), which included adjustment for treatment, visit, treatment by visit interaction, baseline values of age and percent predicted FEV1.
[Source: FDA Biostatistical analyses, Lan Zeng, PhD, calculated from submitted data sets]

As one can see from these descriptive results, the change through week 24 is similar to that of the FAS, if not slightly better.

3.6 Supportive Analyses

Additional support for a positive treatment effect of ivacaftor in patients with an *R117H-CFTR* mutation can be seen in additional data from Study 110, as well as that from the interim analysis for a subgroup of Study 112. These will be described in the sections below.

STUDY 110 Week 24 through Follow-up Visit (Week 27-28)

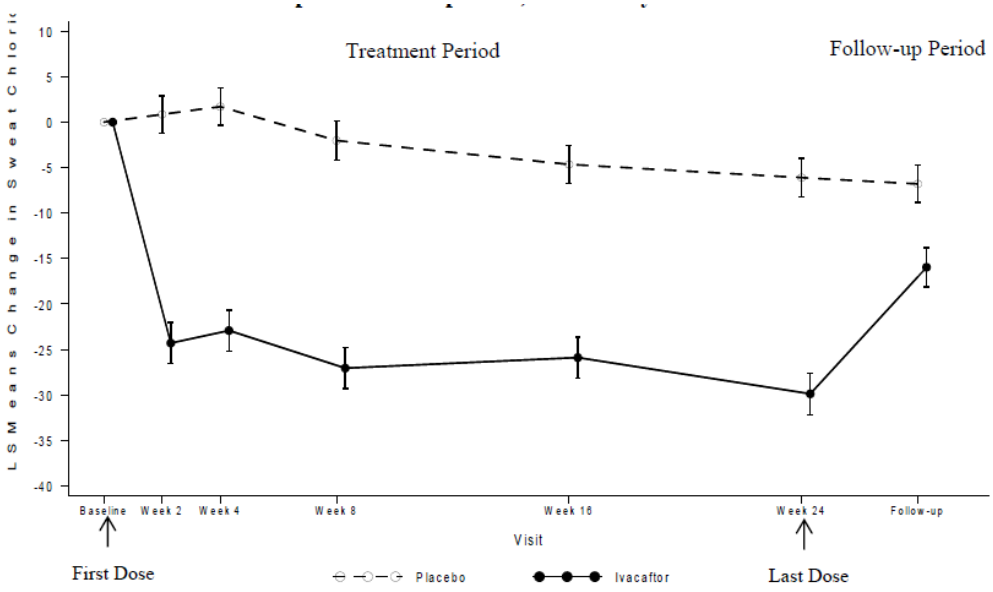
As described above, patients in Study 110 were followed through 24 weeks of treatment. The study design also included a three to four-week wash out period, after which time patients were re-assessed at the Follow-up Visit, with the efficacy endpoints of FEV1, CFQ-R respiratory domain, BMI, and sweat chloride concentration. All patients receiving study drug at study end were evaluated at the follow-up visit, 3 to 4 weeks after study drug was discontinued. (For eight patients, this occurred before week 24; see Section 3.8 Additional Efficacy Issues/Analyses for further details.)

When evaluating the endpoint of change from baseline in percent predicted FEV1, one can see in Figure 3: Primary Endpoint: Absolute Δ from Baseline FEV1 % Predicted, Study 110 FAS (shown earlier in this review), that, for those patients who received ivacaftor through week 24, there is a decline in FEV1 across the washout period to the Follow-up Visit. This pattern is not seen with the placebo-treated group, and suggests a withdrawal of a positive treatment effect.

Likewise, this pattern is replicated in Figure 5: Mean Absolute Δ from Baseline in CFQ-R Respiratory Domain Scores. A similar decline in CFQ-R respiratory domain scores for patients who had received ivacaftor, and then washed out after Week 24, further supports this withdrawal.

Withdrawal of ivacaftor also resulted in loss of the pharmacodynamic effect on sweat chloride. As seen in Figure 7 below, the mean change in sweat chloride for patients who received ivacaftor worsens at the end of treatment, and approaches the prior baseline, and the mean value for those who received placebo (although the mean does not reach the prior baseline value by 3-4 weeks after ivacaftor discontinuation).

Figure 7: Mean Absolute Δ from Baseline in Sweat Chloride to Follow up, FAS



[Source Module 5.3.5.1, CSR 110, Figure 11-3, p 133]

Taken together, the demonstration of values returning toward the baseline mean values once ivacaftor treatment was withdrawn is supportive of ivacaftor providing an effect, albeit smaller than those measured for other CF populations (see accompanying prescribing information).

STUDY 112

Study 112 is the ongoing Phase 3, two-arm, multicenter, open-label, rollover study conducted in subjects with CF who had previously been enrolled in Study 110, as well as those from Study VX12-770-111 (Study 111; subjects with a *non-G551D-CFTR* gating mutation), or Study VX12-770-113 (Study 113; subjects who have phenotypic or molecular evidence of "residual CFTR function"). The Applicant conducted an interim analysis at week 12 consisting of data only from the subgroup of 65 patients from Study 110 who continued on into open label ivacaftor use after a 28-day washout period from Study 110 (including the 8 patients who did not complete 24 weeks' treatment due to the early termination of Study 110). Of these 65 patients, one (iva/iva) discontinued treatment between weeks 2 and 12 (moved from UK to US); 3 others (1-placebo/iva, 2-iva/iva) discontinued at or after week 12. Of those three, one (iva/iva) discontinued due to a CF exacerbation, and two discontinued because they wished to become pregnant.

Data from 62 patients after 12 weeks of open-label treatment, from the baseline assessment (taken after 3-4 weeks of washout from Study 110) to week 12 for both prior treatment groups, demonstrates a median improvement in absolute change in percent predicted FEV1 of 5.5% (min -6.1%, max 49.7%), as shown in Table 20, below. The data suggest a persistent improvement on treatment for all patients, regardless of their prior ivacaftor use in Study 110.

Table 20: Absolute Δ %predicted FEV1, Study 112 FAS

Study Visit	Statistic	Placebo/Ivacaftor (Percentage Points)	Ivacaftor/Ivacaftor (Percentage Points)	Overall (Percentage Points)
Baseline	N	35	30	65
	Mean (SD)	70.9964 (21.47051)	72.6868 (19.45402)	71.7766 (20.42321)
	Median	70.1690	72.6600	72.3350
	Min, Max	30.601, 113.246	34.939, 101.724	30.601, 113.246
Week 2	N	35	30	65
	Mean (SD)	3.2399 (6.70765)	4.4609 (9.36423)	3.8034 (8.00078)
	Median	2.7400	2.8080	2.7760
	Min, Max	-6.370, 28.476	-5.725, 47.989	-6.370, 47.989
Week 12	N	35	27	62
	Mean (SD)	4.9976 (7.67196)	6.0413 (10.41802)	5.4521 (8.90728)
	Median	2.5450	3.3150	3.0000
	Min, Max	-5.627, 32.158	-6.129, 49.720	-6.129, 49.720

Source: Table 14.2.1.1
FEV_1: forced expiratory volume in 1 second; Max: maximum; Min: minimum; SD: standard deviation
Notes: Baseline is defined as the most recent measurement prior to intake of the first dose of study drug in Study 112. Calculation of change is change from baseline in all cases.

[Source Module 5.3.5.2, CSR 112, Table 4-1, p 19]

Responder analysis of the 65 patients to Week 12 is also represented below in Table 21; one can see that 31% of the total patients in Study 112 achieved an absolute change in percent predicted FEV1 equal or greater than 5%, with 10 patients each from the Study 110 allocations meeting this criterion.

Table 21: Responder Analysis, Absolute Δ from Baseline FEV1 % Pred, Study 112

Category	Placebo/Ivacaftor N = 35 N (%)	Ivacaftor/Ivacaftor N = 30 N (%)	Overall N = 65 N (%)
<3.5%	21 (60.0)	18 (60.0)	39 (60.0)
≥3.5%	14 (40.0)	12 (40.0)	26 (40.0)
<5%	25 (71.4)	20 (66.7)	45 (69.2)
≥5%	10 (28.6)	10 (33.3)	20 (30.8)
<7.5%	27 (77.1)	24 (80.0)	51 (78.5)
≥7.5%	8 (22.9)	6 (20.0)	14 (21.5)
<10%	31 (88.6)	26 (86.7)	57 (87.7)
≥10%	4 (11.4)	4 (13.3)	8 (12.3)

Source: Table 14.2.1.4
FEV_1: forced expiratory volume in 1 second
Note: Absolute change through Week 12 is the average change from baseline over 12 weeks for percent predicted FEV_1.
[Source Module 5.3.5.2, CSR 112, Table 4-3, p 22]

So the data from Study 112 suggests a positive effect in FEV1 for the overall R117H patient population, which supports the small, but not statistically significant effect noted in Study 110. In addition, changes in sweat chloride concentrations and CFQ-R respiratory domain scores can also be seen within this interim analysis data of Study 112, shown below in Table 22, below.

Table 22: Interim Analysis, Efficacy Endpoints for Open Label Study 112, FAS

Variable		Placebo/ ivacaftor	Ivacaftor/ ivacaftor	Total
Interim Results at Week 12				
Absolute Δ from Study 112 Baseline in % predicted FEV1 at Week 12	N **Mean** (SD) Median (Min/max)	35 **4.99** (7.67) 2.55 (-5.6, 32.2)	27 **6.04** (10.42) 3.32 (-6.13, 49.72)	62 **5.45** (8.91) 3.00 (-6.13, 49.72)
Absolute Δ from Study 112 Baseline in Sweat Chloride at Week 12	N **Mean** (SD) Median (Min/max)	33 **-20.9** (9.1) -18.0 (-41.0, -0.5)	26 **-17.2** (12.3) -19.0 (-43.5, 6.0)	59 **-19.3** (10.7) -18.0 (-43.5, 6.0)
Interim Results at Week 2				
Absolute Δ from Study 112 Baseline in CFQ-R Respiratory Domain Score at Week 2	N **Mean** (SD) Median (Min/max)	35 **8.2** (14.0) 5.6 (-22.2, 44.4)	29 **15.7** (21.4) 16.7 (-27.8, 61.1)	64 **11.6** (18.0) 11.1 (-27.8, 61.1)
Source: Module 5.3.5.2, Interim Analysis CSR Study 112, Tables 4-1, 4-4, 4-5]				

These data from studies 110 and 112 replicate small but consistent effects in this patient population.

3.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

The data from the open-label Study 112 has been discussed above. As noted, although all patients were given open-label treatment with ivacaftor, there does appear to be a persistence of effect for an additional 12 weeks for those who received ivacaftor in Study 110, and a benefit for those who received placebo in 110, in terms of FEV1, as well as sweat chloride and CFQ-R respiratory domain, as shown in Table 22 above.

The initial finding of pediatric patients having a negative effect in lung function is not replicated within this open-label data; the Applicant's table is presented below, of absolute change in percent predicted FEV1 from baseline to week 2 and 12, for children aged 6 to 11 years; the group demonstrates benefits overall at weeks 2 and 12.

Table 23: Absolute Δ from Baseline to Weeks 2 and 12 in Percent Predicted FEV1 for 6-11yo, Study 112 Open-Label Data

Study Population	Study Visit	N	Mean Change from Baseline (Percentage Points)	*P* value[a]
Overall	Week 2	15	3.4234	0.3246
	Week 12	15	6.4713	0.0806
Placebo/Ivacaftor	Week 2	8	-1.8155	0.0346
	Week 12	8	3.5778	0.2334
Ivacaftor/Ivacaftor	Week 2	7	9.4107	0.2074
	Week 12	7	9.7781	0.1978

Source: Module 5.3.5.2/VX12-770-112/Table 2-5
Notes: Baseline was defined as the most recent measurement before intake of the first dose of study drug in Study 112. This measurement was taken at the Day 1 Visit for Study 112, which was also the Follow-up Visit of Study 110, and which occurred 3 to 4 weeks after the last dose of study drug in Study 110). Age is the baseline age in Study 110.
[a] *P* values are based on the one-sample t-test.

[Source Module 5.3.5.2, CSR 112, Table 13, p 46]

3.8 Additional Efficacy Issues/Analyses

The Applicant made the decision to discontinue enrollment and stop study 110 early, despite the Data Monitoring Committee's recommendation to continue enrollment. Because eight of the 69 patients (12% of the population) stopped treatment before reaching 24 weeks, it is worthwhile to explore the data without those subjects. Primary and key secondary efficacy endpoints are shown in the table below.

Table 24: Efficacy, Patients Who Completed 24 Weeks of Treatment, Study 110

Efficacy Parameter	Placebo		Ivacaftor n=30		Difference vs. Placebo (95%CI)
	n	value	n	value	
Absolute Δ from Baseline Percent Predicted FEV1	31	1.08	30	3.76	2.68 (-0.41, 5.77)
Rate of Δ from Baseline in BMI (kg/m^2)	31	0.23	30	0.39	0.17 (-1.73, 2.07)
Absolute Δ from Baseline in Sweat Chloride (mmol/L)	31	-2.44	28	-27.03	-24.59 (-28.87, -20.30)
Absolute Δ from Baseline in CFQ-R Respiratory Domain score	30	-1.6	29	9.1	10.7 (4.4, 17.1)
[Source: Module 5.3.5.1, CSR Study 110, Table 11-66, Complete Case Set data, page 214]					

The treatment effects of ivacaftor in patients who completed the originally-planned study duration was very similar to that of the full analysis set, in terms of changes in FEV1, sweat chloride, and patient-reported symptom scoring. Thus, the early termination of Study 110, while limiting data collection from eight patients, did not significantly alter results.

4 Review of Safety

Safety Summary

The safety information for ivacaftor is derived from the approved program, as well as from data from Studies 110 and 112. As all the studies were conducted in patients with CF with similar demographics, the data from these two new studies can be viewed in the context of the larger overall safety database for ivacaftor where the overall safety profile has been acceptable.

Specifically, for Studies 110 and 112, safety assessments were adequate and included adverse events, physical examinations, vital signs, ECGs, and clinical laboratory testing. There were a total of 34 patients treated with ivacaftor 150 mg every 12 hours, and 35 patients treated with placebo. The mean treatment duration was similar between the treatment groups with mean 151 days for the ivacaftor group and 155 days for those who received placebo.

The 24-week data from Study 110, and 12 weeks' open label interim data from Study 112, in patients with an *R117H-CFTR* mutation, appears adequate to allow for a determination of safety in the proposed population.

No deaths were reported during the placebo-controlled trial, and SAEs were within what would be expected for a CF population, including CF exacerbations (and other respiratory, GI, and infectious concerns). There were few SAEs overall, and fewer

SAEs reported in the ivacaftor-treated group (12%) than in the placebo group (17%). Review of additional safety data from the open-label extension demonstrated no concerns, and there were no new safety signals identified.

Dropout and discontinuation data provided numbers overall that were small, and do not suggest any specific safety issue or signal. The overall incidence of drug interruption was similar between these small treatment groups, with 2 of the placebo patients and 1 of the ivacaftor patients interrupting study drug for events.

Two potential safety concerns identified in the ongoing global ivacaftor clinical development program include elevations in hepatic enzymes, and the potential development of lens opacities (cataracts) in younger children. These were pre-specified AEs of interest in the Applicant's clinical *R117H* program. The Applicant provided adequate monitoring of liver function in these trials. There were two placebo patients and 4 ivacaftor-treated patients who demonstrated changes in transaminases greater than 2 times the upper limit of normal at any time throughout the treatment period. These events are not outside what is expected of ivacaftor from the approved indications, nor what might be expected for CF patients in general. Therefore, the data with regard to liver safety is reassuring, and does not represent a significant safety concern for the use of ivacaftor in the *R117H* patient population.

The potential for cataracts was identified in the ivacaftor program after initial approval in the *G551D* population, on the basis of nonclinical findings of lens opacities in juvenile rat studies. From the data collected in Study 110, there were no clinically relevant changes in ophthalmologic exams, and no reports of cataract development during Study 110.

The common adverse event profile is similar to that already labeled for ivacaftor, with upper respiratory and abdominal symptoms at slightly increased rates over placebo, none of which pose a serious safety risk. In addition, no significant or new safety risks were identified for the pediatric patient population seen within Study 110. Overall, the safety risks of ivacaftor within the *R117H* population are relatively small, and provide no additional concerns to the known safety profile of ivacaftor in patients with CF.

4.1 Methods

4.1.1 Studies/Clinical Trials Used to Evaluate Safety

There are a total of 26 studies submitted to this NDA which provide the overall safety database for ivacaftor. 23 of these studies were evaluated in the original Application (efficacy and safety in CF patients with a *G551D* mutation), and one study was reviewed under sNDA-4 (efficacy and safety in 8 additional similar CF mutations), which provide the bulk of the safety database, and are described in current approved labeling.

Two studies were submitted under this supplement specific to the *R117H-CFTR* patient population, to be discussed below.

Study 110 is a randomized, placebo-controlled trial, which provides the majority of the safety data described here for the *R117H-CFTR* patient population. Additional major safety data from an interim analysis to week 12 is provided for only those patients who participated in Study 110 and subsequently rolled into open-label extension Study 112 (a sub-group of the total Study 112 population, measured at an early time point).

For the purposes of this review, the data from Study 110 will be evaluated in the context of the known safety profile of ivacaftor in patients with CF who carry *CFTR* gene mutations other than *R117H.*

4.1.2 Categorization of Adverse Events

Within the *R117H* development program, the Applicant defined adverse event (AE) as any untoward medical occurrence in a patient during the study, which does not require a causal relationship with study drug, and whether or not it is considered to be study drug-related. It includes any newly occurring event, or previously-existing condition that has increased in severity. This AE definition is consistent with that used throughout the entire ivacaftor program.

The definition of "clinically significant assessments" has evolved, however, and for the *R117H* program, was defined as any laboratory assessment, ECG, vital sign or physical exam finding that was judged by the investigator as clinically significant worsening from baseline, thus were to be reported as adverse events. Further, it was specified that, when possible, a clinical diagnosis for the assessment should be noted, but in the absence of diagnosis, the assessment itself should be reported as the AE. The definition of "clinically significant" abnormal study assessment meets at least one of the following:

- Concomitant signs or symptoms related to the abnormal assessment
- Further diagnostic testing or medical/surgical intervention
- Change in study drug dose or discontinuation from the study

This provided additional clarity to investigators, and is reasonable.

Adverse events were classified using MedDRA Version 15.1 for all studies.

4.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Study 110 provides the data for which the incidence of adverse events can be evaluated against placebo, and indirectly compared to the full safety database we have from the ivacaftor program. The 65 patients included in the interim analysis data from Study 112 are the same patients continued from Study 110. However, because patients all rolled

over to active treatment, exposures for these groups are different; therefore data from Study 112 will be described separately from that of Study 110, when pertinent.

4.2 Adequacy of Safety Assessments

The studies in this clinical program were well-designed to assess safety of ivacaftor in a general population of CF patients with the *R117H-CFTR* mutation from age 6 and older, and across a range of severity in baseline lung function, which covers a reasonable spectrum of disease.

The program was also designed to evaluate potential concerns identified within the overall ivacaftor program, including evaluation of liver transaminases and monitoring for lens opacities in patients aged 6 to 11 years, based on the potential safety signal for ivacaftor suggested in the non-clinical data, and the subject of an ongoing Post-Marketing Requirement (PMR) for safety for ivacaftor. This population excluded patients with the most severe lung disease (FEV1 <40% predicted), which is reasonable, given that these patients typically have multiple confounding co-morbidities, or due to severity and irreversibility of their lung disease, may be on transplant lists.

Reviewer's Comment:
Note that patient 10-032-01 was included, even though baseline FEV1 was 33% predicted (this is the 42yo female R117H-7T patient with normal sweat chloride, but severe lung disease).

4.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The mean exposure in Study 110 was similar for placebo (155.8 {40.0} days) and ivacaftor (151.1 {46.2} days) treatment groups. Most patients received at least 24 weeks of treatment, and all but 3 patients received at least 4 weeks' treatment.

Table 25: Exposure to Study Drug, Study 110

Number of Weeks of Exposure to Study Drug	Placebo N=35 n (%)	Ivacaftor N=34 n (%)
0 to <2 weeks	0	0
2 to <4 weeks	1 (3%)	2 (6%)
4 to <8 weeks	1 (3%)	2 (6%)
8 to <16 weeks	2 (6%)	0
16 to <24 weeks	7 (20%)	9 (27%)
Greater than or equal to 24 weeks	24 (69%)	21 (62%)

Source: Modified from Table 1 in Module 2.7.4, Summary of Clinical Safety, page 7.

In addition, 65 patients from Study 110 were rolled over into Study 112 (35 from placebo and 30 from ivacaftor); all rolled over into the open-label ivacaftor arm of Study 112. As of the subset interim analysis at week 12, 62 patients were continuing in the open-label extension. Three patients had discontinued, including one patient who moved to a different country, one who discontinued in order to become pregnant, and one who discontinued the study due to SAE of CF exacerbation.

The Demographics of these patients have been described in Section 3.2.2 Demographics, of this review.

4.2.2 Explorations for Dose Response

The Applicant chose the same dose for Study 110 as was used in the overall ivacaftor program. This is reasonable, as the safety and efficacy for the gating mutations has been established. Doses above 150mg are described within approved labeling (See attached prescribing information Section 12.2 Pharmacodynamics, ECG Evaluation), as are the dose ranging data (prescribing information, section 14.1).

4.2.3 Routine Clinical Testing

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries including liver transaminases, coagulation studies, and urinalyses. Testing was adequate and appropriate. No important parameters were left out of evaluations.

4.2.4 Metabolic, Clearance, and Interaction Workup

Information regarding metabolism, clearance, and drug-drug interactions is available in the approved labeling for ivacaftor. It would not be expected to change in this additional subset of CF patients evaluated within this sNDA.

4.2.5 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This section is not applicable, as there are no other drugs in the class.

4.3 Major Safety Results

Table 26 provides a high-level overview of each of the main categories to be discussed; major safety results for Study 110 are described in detail in the sections below.

Table 26: Overview of Safety, Study 110

Safety Finding	Placebo N=35 n (%)	Ivacaftor N=34 n (%)
Deaths	0	0
Patients having at least one SAE	6 (17)	4 (12)
Patients who Discontinued from Study for Any reason[a]	0	2[b] (6)
Patients with any AE leading to Study Drug Discontinuation	0	0
Patients with Any AE leading to Study Drug Interruption	2 (6)	1 (3)
Patients with at least 1 AE Reported	35 (100)	32 (94)

a= Not including patients for whom study was terminated prior to week 24;
b= One patient discontinued at week 2 for non-compliance with ophthalmologic exam, one patient at week 16 for pregnancy.
Source: Module 5.3.5.1, CSR for Study 110, Tables 12-2, 12-10, and sections 12.3.1.1, 12.3.1.2, and 12.3.1.5.

4.3.1 Deaths

No deaths occurred during the conduct of Study 110, nor to date in Study 112. Likewise, no deaths were noted in any of the other 24 studies in the ivacaftor development program.

4.3.2 Nonfatal Serious Adverse Events

The Applicant utilized the appropriate definition of Serious Adverse Event throughout their development program, as defined in 21CFR. Data was evaluated from the Clinical Study report for Study 110, the supplement's Clinical Review of Safety, and post-marketing information provided in Module 5.3.5.3, Integrated Summary of Safety, as well as the full narrative reports of for any patient with an SAE from Study 110, and the interim data from Study 112.

Table 27 below provides a listing of all SAEs seen in Study 110. There were numerically more patients with SAEs in the placebo group than in the treatment group. Of the ten patients with SAEs, eight occurred in the adult (≥18 years) population, including eight episodes of CF exacerbation (6- placebo, 2- ivacaftor), and one episode of cellulitis (ivacaftor). The two remaining patients with SAEs were in the 6-11years group, both of whom were receiving ivacaftor, and consisted of one CF exacerbation and one episode of constipation.

Table 27: Serious Adverse Events, Study 110

	Placebo N=35 n (%)	Ivacaftor N=34 n (%)	Overall N=69 n (%)
All Patients with Any SAE	**6 (17)**	**4 (12)**	**10 (15)**
System Organ Class/Preferred Term			
Infections and Infestations	6 (17)	3 (9)	9 (13)
Infective Exacerbation of CF	6 (17)	3 (9)	9 (13)
Cellulitis		1 (3)	1 (1.4)
Gastrointestinal Disorders		1 (3)	1 (1.4)
Constipation		1 (3)	1 (1.4)

Source: Module 5.3.5.1, CSR Study 110, Tables 12-12, 14.3.2.4, 14.3.2.5ad

In general, the SAEs were within what would be expected for a CF population, with the majority of events being CF exacerbations. Cellulitis and constipation occurred as one event each; constipation is a common finding in patients with CF, and cellulitis is not specific to CF. This is very consistent with the known safety profile of ivacaftor; the original review noted that CF exacerbations were the most frequently noted SAEs, and they occurred more often in placebo patients than in those treated with ivacaftor. The original safety set also had respiratory, GI and metabolic SAEs, but as noted elsewhere in this review, the *R117H* patient population may have a less severe phenotype than those with gating or *F508del*- homozygous mutations, so these results are as would be expected, and reassuring.

SAEs in the Uncontrolled Study 112 Interim Analysis

The interim week 12 data from 65 patients enrolled in the ivacaftor arm of Study 112 who rolled over from Study 110, was evaluated for SAEs. Using a cutoff date of April 07, 2014, 12 SAEs were identified in 8 patients. Nine of these episodes were infective pulmonary exacerbations of CF; two events were in patients who had received placebo in Study 110, and were receiving ivacaftor in Study 112, and the remaining 7 events were patients in the ivacaftor/ivacaftor treatment group. Of the 3 remaining SAEs, one subject had and SAE of “influenza,” and another subject had SAEs of angioedema and urticaria (at day 91 of ivacaftor treatment, ivacaftor was continued and event resolved). All but one of these SAEs was considered “not related” by investigators; the one case deemed “possibly related” was a CF exacerbation in a 9yo girl, for whom ivacaftor treatment was discontinued. She had received a total of 341 days of ivacaftor treatment (ivacaftor/ivacaftor group), and the event was associated with a new acquisition of Methicillin-resistant *Staphlococcus aureus* (MRSA) infection.

Overall, the SAE reports collected to date from Study 112 do not suggest any new or concerning safety signals, and are in line with the ivacaftor program as a whole.

4.3.3 Dropouts and/or Discontinuations

Discontinuations due to Adverse Events

There were no patients who discontinued Study 110 due to Adverse Events (AE).

Patients who Did Not Complete To 24 Weeks/ Permanent Discontinuations

Eight patients were deemed to have "completed" the study prior to week 24 due to early study termination; all were enrolled into Study 112. In addition, two patients were discontinued from Study 110, as follows:

- Patient [10-033-02], a 13yo girl who received ivacaftor, was discontinued at visit 2 because of non-compliance in completing the required ophthalmologic exam at screening.
- Patient [10-23-01], a 32 year old woman who received ivacaftor, discontinued the study after week 16 evaluations, due to pregnancy.

These two cases do not affect the overall safety profile of ivacaftor.

Patients with Adverse Events Leading to Study Drug Interruption

There were 3 patients who had interruptions in their study drug during Study 110, as follows:

- One adult patient [10-012-03] in the ivacaftor group had an SAE of infective exacerbation of CF for which study drug was temporarily interrupted. Treatment resumed when the patient recovered; the event was deemed "not related."
- One adult patient [10-044-01] in the placebo group had AEs of gastroenteritis, dehydration, and hypokalemia, for which study drug was interrupted. Treatment resumed when the patient recovered; the event was deemed "not related."
- One 8-year old boy [10-071-03] in the placebo group had AEs of vomiting and diarrhea, for which study drug was interrupted. Treatment resumed when the patient recovered; the event was deemed "possibly related."

These 3 cases do not affect the safety profile of ivacaftor, and are consistent with CF disease, and the ivacaftor safety database.

4.3.4 Submission Specific Primary Safety Concerns

The Applicant did not pre-specify any "events of interest" for Study 110, but did have specific rules regarding elevations in liver function parameters and language regarding contraception and pregnancy, which were acceptable, based on the overall safety profile of ivacaftor in CF populations.

4.3.4.1 Pregnancy

There was one reported pregnancy during the conduct of Study 110, which led to the patient's early discontinuation as noted above. The patient had a history of premature rupture of membranes, so had a cervical cerclage placed at 14 weeks' gestational age (GA). She was admitted to the hospital for cervical insufficiency at 15 weeks' GA, developed gestational diabetes at 25 weeks/5 days GA, and delivered via C-section at week 28 due to premature rupture of membranes. The baby was reported as "healthy." The Investigator did not consider cervical insufficiency and gestational diabetes to be adverse events.

No pregnancies have been noted in Study 112.

4.3.4.2 Elevations in Transaminases/ Parameters of Liver Function

Within the safety database for ivacaftor, elevations in transaminases were noted. For this reason, transaminase values were monitored closely in Study 110. Included below in Table 28 are the results of maximum on-treatment transaminase and bilirubin levels for all patients. There were no major elevations >5x the upper limit of normal (ULN) noted for patients in either treatment group. Only one patient in each treatment group had a maximum ALT value of >3 to $\leq$5x ULN, and one placebo patient demonstrated an increase in ALT >2to $\leq$3x ULN, whereas in the ivacaftor group, there were 2 patients with maximum ALT and one patient with AST maximum that fell within >2to $\leq$3x ULN.

The Interim analysis of ongoing Study 112 did not assess these parameters, focusing only on serious adverse event data.

Overall, these findings are consistent with the small differences in transaminases seen within the global ivacaftor safety database, and are reassuring for the *R117H* population.

Table 28: Maximum On-Treatment LFT Results, Safety Set, Study 110

Maximum On-Treatment Result	Liver Function Test	Placebo N = 35 n (%)	Ivacaftor N = 34 n (%)
≤2 × ULN	ALT (U/L)	33 (94.3)	31 (91.2)
	AST (U/L)	35 (100.0)	33 (97.1)
	Total bilirubin (µmol/L)	35 (100.0)	34 (100.0)
>2 × ULN to ≤3 × ULN	ALT (U/L)	1 (2.9)	2 (5.9)
	AST (U/L)	0	1 (2.9)
	Total bilirubin (µmol/L)	0	0
>3 × ULN to ≤5 × ULN	ALT (U/L)	1 (2.9)	1 (2.9)
	AST (U/L)	0	0
	Total bilirubin (µmol/L)	0	0
>5 × ULN to ≤8 × ULN	ALT (U/L)	0	0
	AST (U/L)	0	0
	Total bilirubin (µmol/L)	0	0
>8 × ULN	ALT (U/L)	0	0
	AST (U/L)	0	0
	Total bilirubin (µmol/L)	0	0

Source: Table 14.3.4.10.
ALT: alanine transaminase; AST: aspartate transaminase; LFT: liver function test; N: total number of subjects; n: number of subjects with an observation; ULN: upper limit of normal.
Notes: Baseline is defined as the most recent measurement before intake of the first dose of study drug. The result categorized is the maximum of all post baseline LFT results occurring on or before the Week 24 Visit.

[Source: Module 5.3.5.1, CSR Study 110, Table 12-15]

4.3.4.3 Cataracts

Because of a finding of dose-related increase of lens opacities in the non-clinical juvenile rat studies (as noted in the ivacaftor prescribing information), and the potential safety concern for patients, the Applicant included ophthalmologic exams for all patients at screening. In addition, a second evaluation was conducted specifically for children aged 6 to 11 years, planned at the Week 24 visit (or early termination, as applicable). For the 19 patients evaluated with a second examination (9 placebo, 10 ivacaftor), there were no significant changes in visual acuity over the 24-week study period, and no patients were noted to have a change to “abnormal” in their slit lamp assessments. Likewise, no patients developed lens opacities during Study 110. [Source: Module 5.3.5.1, CSR 110, Section 12.5.3 p 257-258, Table 12-20; Tables 14.3.7, 14.3.8].

This lack of ophthalmologic findings in the pediatric patients was somewhat reassuring (acknowledging that the 24-week duration would be short for development of cataracts), and consistent with the lack of clinical ophthalmologic findings in the original *G551D* program. A long-term ocular safety study in pediatric patients is ongoing.

4.4 Supportive Safety Results

4.4.1 Common Adverse Events

Common adverse events for patients with an *R117H-CFTR* allele are described below. Adverse events were evaluated at every clinic visit throughout the 24-week treatment period in Study 110. All patients were queried, using non-leading questions, about the occurrence of adverse events at each visit. All spontaneously reported adverse events were also collected. Adverse events were recorded as indicated by the protocol, and described by duration, severity, seriousness, investigator's opinion of relatedness to study drug, action taken toward study drug, outcome, and concomitant therapy use. This was consistent with the methods for collecting AEs throughout the ivacaftor development program.

Almost every patient enrolled in Study 110 reported at least one adverse event, which is not unexpected with an underlying disease process such as cystic fibrosis. Table 29, listed below, demonstrates the number of patients that reported adverse events which occurred in at least 10% of patients in any treatment group. The highest rates of incidence occur in those system-organ classes (SOCs) and preferred terms (PTs) which would be expected to have events for this patient population, and include respiratory, infectious, GI, and general disorders.

By PT, the adverse events with the highest incidence in both treatment groups were infective pulmonary exacerbation of CF (38.2% of subjects in the ivacaftor group and 40.0% of subjects in the placebo group) and cough (29.4% of subjects in the ivacaftor group and 25.7% of subjects in the placebo group).

The incidences of sputum increased, nasal congestion, oropharyngeal pain, wheezing, diarrhea, abdominal pain, and headache were >10% in the ivacaftor group. The incidences of upper respiratory tract infection, sinusitis, sputum increased, hemoptysis, diarrhea, vomiting, pyrexia, headache, and arthralgia were >10% in the placebo group.

These events and their incidences are similar to the safety data from the ivacaftor programs in patients with *G551D*, other gating, and *F508del*-homozygous mutations which have been evaluated in the ivacaftor development safety database. No new events are identified; this is reassuring, and supports the safety for the subset of patients who carry an *R117H* mutation in *CFTR*.

Table 29: Adverse Events Occurring in at Least 10% of Patients by System Organ Class and Preferred Term, Study 110

System Organ Class Preferred Term	Placebo N=35	Ivacaftor N=34
Subjects with Any AE	35 (100)	32 (94)
Infections and Infestations	24 (69)	21 (62)
Infective pulmonary exacerbation of CF	14 (40)	13 (38)
Upper respiratory tract infection	5 (14)	3 (9)
Sinusitis	5 (14)	2 (6)
Respiratory, Thoracic & Mediastinal Disorder	19 (54)	18 (53)
Cough	9 (26)	10 (29)
Sputum increased	4 (11)	5 (15)
Nasal congestion	2 (6)	5 (15)
Oropharyngeal pain	2 (6)	5 (15)
Wheezing	1 (3)	4 (12)
Hemoptysis	6 (17)	0
Gastrointestinal Disorders	13 (37)	13 (38)
Diarrhea	4 (11)	5 (15)
Abdominal Pain	0	4 (12)
Vomiting	4 (11)	3 (9)
General Disorder & Admin. Site Condition	11 (31)	7 (21)
Pyrexia	6 (17)	2 (6)
Nervous System Disorders	9 (26)	6 (18)
Headache	5 (15)	6 (18)
Musculoskeletal and Connective Tissue Dis.	8 (23)	2 (6)
Arthralgia	4 (11)	0
[Source: Module 5.3.5.1, CSR 110, Table 12-3; Table 14.3.1.2.1]		

The incidence of adverse reactions that occurred at least 5% more often in the ivacaftor group than in placebo, are demonstrated in Table 30, below. Like the overall adverse events, these adverse reactions are not unexpected, and are similar to the events noted in the full ivacaftor safety program to date.

Table 30: Adverse Reactions Occurring in Ivacaftor Patients at an Incidence of ≥5% over Placebo, Study 110

	Placebo N=35 (%)	Ivacaftor N=34 (%)	Difference in Incidence over placebo (%)
Patients with Any AE Reported	35 (100)	32 (94)	---
Event by Preferred Term			
Abdominal pain/ discomfort[a]	0	6 (18)	18
Nasal congestion	2 (6)	5 (15)	9
Oropharyngeal pain	2 (6)	5 (15)	9
Wheezing	1 (3)	4 (12)	9
Upper airway cough syndrome	0	3 (9)	9
Influenza-like illness	0	2 (6)	6

a= Preferred terms Abdominal pain (0 placebo vs. 4 iva) and abdominal discomfort (0 placebo vs. 2 iva) were combined
[Source: Module 5.3.5.1, CSR 110, Tables 14.3.1.3, 14.3.1.8.1]

When considered in the broad context of the ivacaftor development program, safety from Study 110 is reassuring, and presents no new concerns.

4.4.2 Safety of Study 110 by Age Subgroups

The Applicant initially proposed an indication for patients aged ≥18 years with an *R117H* mutation in *CFTR*, based on efficacy findings. After the NDA was submitted, the Applicant requested a change in the indication to extend to the entire population aged 6 and older. Because of the negative change in FEV1 for children aged 6 to 11 years, it is important to evaluate safety findings for this population as well. Data from the 2 patients aged 12 to 17 years is not included, since one patient received placebo, and the other patient who received ivacaftor [patient 10-033-02] was discontinued at week 2 due to non-adherence with ophthalmologic exam according to the protocol.

Table 31 below lists the most common AE across ages and treatment groups. All events within the 6 to 11 year age group (except ADHD) have been described in the ivacaftor safety database, or are common findings with CF disease. (ADHD is not unexpected finding in a pediatric population, and does not raise concern, especially because the two pediatric patients received placebo treatment). Of these events reported in the pediatric group, none occur in more than 2 patients within a treatment group, which provides some reassurance that there are no significant safety findings that would correlate with a decline in pulmonary function that was noted in the subgroup analysis. For example, only 2 of the 9 children who received ivacaftor reported a CF exacerbation during the 24 week treatment period. If a majority of children had CF exacerbations reported, and had a decline in FEV1 as well, that might have raised a specific safety concern in this CF subset. As demonstrated, however, there are no new safety findings, or events that would not be expected as part of the ivacaftor safety database, or part of the CF spectrum of disease.

Table 31: Adverse Events Occurring in At Least 15% of Patients in Either Treatment Group, by Age and PT, Safety 110

System Organ Class Preferred Term	Age >18 years		Age 6 to 11 years	
	Placebo N=26 (%)	Ivacaftor N=24(%)	Placebo N=8(%)	Ivacaftor N=9(%)
Subjects with Any AE	26 (100)	23 (96)	8 (100)	9 (100)
Subjects with Any SAE	6 (23)	2 (8)	0	2 (22)
Infections and Infestations	19 (73)	16 (67)	5 (62)	5 (56)
Infective pulmonary exacerbation of CF	13 (50)	11 (46)	1 (13)	2 (22)
Bacterial disease carrier	1 (4)	1 (4)	0	2 (22)
Upper respiratory tract infection	5 (19)	2 (8)	0	1 (11)
Sinusitis	3 (12)	1 (4)	2 (25)	1 (11)
Respiratory, Thoracic & Mediastinal Disorder	14 (54)	16 (67)	4 (50)	2 (22)
Cough	7 (27)	9 (38)	1 (13)	1 (11)
Sputum increased	4 (15)	5 (21)	0	0
Nasal congestion	1 (4)	5 (21)	1 (13)	0
Oropharyngeal pain	0 4 (17)	4 (17)	2 (25)	1 (11)
Wheezing		4 (17)	0	
Hemoptysis	6 (23)	0	0	0
Gastrointestinal Disorders	10 (39)	9 (38)	3 (38)	4 (44)
Diarrhea	3 (12)	4 (17)	1 (13)	1 (11)
Abdominal Pain	0	2 (8)	0	2 (22)
Abdominal pain upper	0	1 (4)	2 (25)	1 (11)
General Disorder & Admin. Site Condition	8 (31)	5 (21)	2 (25)	2 (22)
Pyrexia	3 (12)	1 (4)	2 (25)	1 (11)
Nervous System Disorders	7 (27)	4 (17)	1 (13)	2 (22)
Headache	3 (12)	4 (17)	1 (13)	2 (22)
Psychiatric Disorders.	1 (4)	0	2 (25)	0
Attention-Deficit/Hyperactivity	0	0	2 (25)	0

[Source: Module 5.3.5.1, CSR 110, Table 12-4; Table 14.3.1.2.2, 14.3.2.4, 14.3.2.5ad, listing 16.2.4.1, 16.2.7.1]

4.4.3 Laboratory Findings, Vital Signs, ECGs

There were no clinically important trends identified in clinical laboratory results (serum chemistry, hematology, coagulation studies, urinalysis), vital signs (heart rate, blood pressure, temperature, respiratory rate), or ECGs that were attributable to ivacaftor use. This is reassuring, and consistent with what was seen within the ivacaftor clinical program to date.

4.5 Other Safety Explorations

Other safety explorations, such as time dependency for AEs, drug-demographic, and drug-drug interactions have been characterized in the ivacaftor development program, and are described in the ivacaftor prescribing information. The data provided within this supplement does not suggest any variances from what is known of ivacaftor in other CF populations.

5 Postmarket Experience

Post-market safety information of ivacaftor includes information from over 1,900 patients with CF who have received at least one dose of ivacaftor since its international birth date (January 31, 2012), through a cutoff date of January 23, 2014. Overall, post-marketing data are consistent with data collected within the development program's clinical trials which are described in the prescribing information, and support the established safety profile of ivacaftor.

A post-marketing study is currently being conducted to further evaluate ivacaftor with regard to ocular safety in patients with CF aged 6 to 12 years of age, based on the non-clinical findings of dose-dependent cataract development in juvenile animal studies. In children who have been receiving commercially-available ivacaftor, there have been post-marketing safety reports of cataracts or lens abnormalities. Some of these patients (5) were identified within the observational PMR Safety study, which is ongoing; two cases were spontaneous reports, and two patients were identified at the end of the original Study 105, which was the open-label, long-term safety study for patients with a *G551D-CFTR* mutation. These reports are confounded in most cases by complex medical history including prior use of steroids, positive family history of cataracts, and no baseline ophthalmologic exam prior to initiation of ivacaftor. In some cases, the reports clearly document that lens opacities were consistent with congenital cataracts. This potential safety concern will be more fully understood when results from the observational PMR ocular safety study become available.

6 Literature Review/References

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE
FOR IVACAFTOR ORAL TABLETS (KALYDECO)
NDA 203-188 SUPPLEMENT 14

Statistical briefing material for the Pulmonary-Allergy Drugs Advisory Committee
October 21, 2014

Thomas Permutt
Director, Division of Biometrics II

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1 INTRODUCTION

Cystic fibrosis is a disease affecting mainly the lungs that is caused by any of dozens or hundreds of different genetic mutations. Ivacaftor was first approved for a single mutation known as G551D, which occurs in approximately 4% of patients in the U.S. A supplement was approved for a group of eight other mutations with common features, but not for a ninth mutation included in the same study. The present supplement covers another mutation known as R117H. The supplement reports a single controlled study (110) along with data from an open-label extension study (112) for those patients who had been in study 110.

Study 110 failed with respect to its primary analysis, testing for a difference in pulmonary function between active and placebo groups averaged over 24 weeks. Afterward, the applicant found a significant difference for the subgroup of patients over 18 years old, and they sought to expand the indication to include that subgroup. After conversations with the Agency, however, the proposed indication was revised to include pediatric patients notwithstanding the unfavorable results in the pediatric patients in study 110.

2 STUDY 110

2.1 PRIMARY ANALYSIS

Study 110 was a randomized, double-blind, placebo-controlled study of 24 weeks' duration. The primary measure of outcome was "the absolute change from baseline in percent predicted FEV1 through week 24," interpreted as follows: FEV1 is the forced expiratory volume in the first second of a spirogram. FEV1 is often normalized by dividing by a predicted value based on the subject's height, age, sex, weight, and ethnicity. Sometimes this ratio is further normalized by dividing the change over the course of the study by the baseline value, but it was not in this case, hence "absolute." "Through week 24" means an average of measurements at weeks 2, 4, 8, 16, and 24, as represented by the main effect of treatment in a mixed-effects model for repeated measures (MMRM). The results are shown in the table below (clinical study report, p. 126).

Table 11-1 Absolute Change From Baseline in Percent Predicted FEV_1 by MMRM, Full Analysis Set

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	N	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	35	70.2315	--	--	--	--
	Ivacaftor	34	75.6968	--	--		
Overall Post-baseline	Placebo	35	71.1264	35	0.4611	2.1114 (-1.1305, 5.3532)	0.1979
	Ivacaftor	34	78.0432	34	2.5724		

Source: Table 14.2.1.2.1.
Note: Sample statistics are unadjusted results. Difference is ivacaftor – placebo. A positive difference favors ivacaftor.
[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24) and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of age and percent predicted FEV_1 using compound symmetry covariance matrix.

The applicant notes, however, an apparent differential effect by age. The effect is nominally significant in patients over 18 and also nominally significant in the wrong direction in patients under 12. (There were very few patients between 12 and 18. Tables are from pp. 159, 176.)

Table 11-29 Absolute Change From Baseline in Percent Predicted FEV_1 by MMRM; Full Analysis Set, Subjects ≥18 Years of Age

Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	26	62.2149	--	--	--	--
	Ivacaftor	24	67.0287	--	--		
Overall Post-baseline	Placebo	26	62.1157	26	-0.4567	4.9647 (1.1497, 8.7796)	0.0119
	Ivacaftor	24	71.6227	24	4.5080		

Sources: Table 14.2.1.2.4, Table 14.2.1.2.2.2ad, Table 14.2.1.2.4.1ad, and Table 14.2.1.2.4.2ad.
Note: Sample statistics are unadjusted results. Difference is ivacaftor – placebo. A positive difference favors ivacaftor.
[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24) and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of percent predicted FEV_1 using compound symmetry covariance matrix.

Table 11-41 Absolute Change From Baseline in Percent Predicted FEV_1 by MMRM; Full Analysis Set, Subjects 6 to 11 Years of Age (Inclusive)

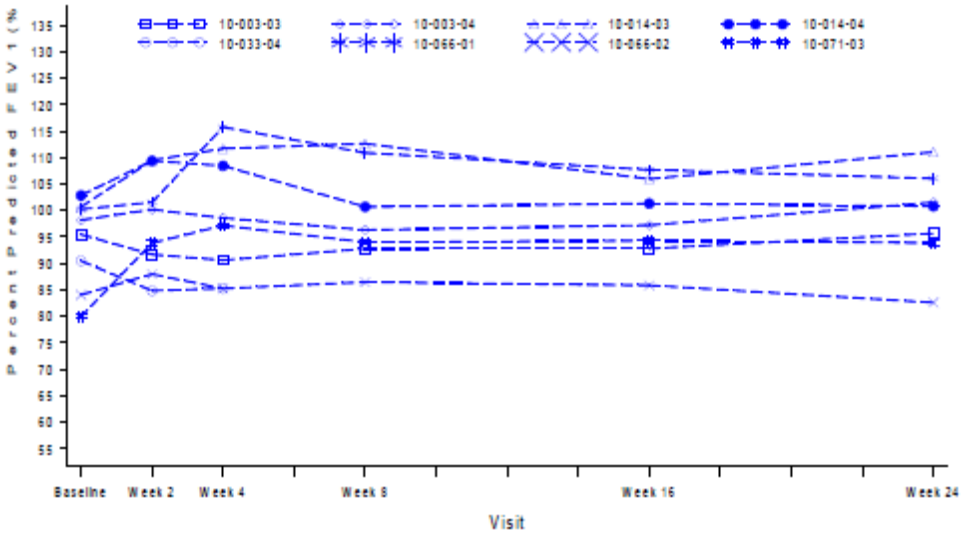
Visit or Time Period	Treatment Group	Sample Statistics		Absolute Change From Baseline[a]		Treatment Effect (Ivacaftor vs Placebo)	
		n	Mean	n	LS Mean	Difference (95% CI)	*P* value
Baseline	Placebo	8	93.9806	--	--	--	--
	Ivacaftor	9	97.4854	--	--		
Overall Post-baseline	Placebo	8	98.4296	8	3.5101	-6.3334 (-11.9602, -0.7066)	0.0301
	Ivacaftor	9	96.2475	9	-2.8233		

Sources: Table 14.2.1.2.4, and Table 14.2.1.2.2.1ad.
Notes: Sample statistics are unadjusted results. Difference is ivacaftor – placebo. A positive difference favors ivacaftor.
[a] Estimates were obtained from MMRM with absolute change from baseline as the dependent variable; with treatment group, categorical visit (Weeks 2, 4, 8, 16, and 24) and treatment by visit interaction as fixed effects; with subject as a random effect; and with adjustment for the continuous baseline value of percent predicted FEV_1 using compound symmetry covariance matrix.

The applicant interprets these findings together as evidence of a positive effect on pulmonary function in adults and a chance negative outcome in children. They note the improvement from baseline in the pediatric placebo group as well as a single especially bad outcome in the active group for a patient who had an exacerbation (figures below, p 182). The anomalous observation is not highly influential in the MMRM analysis, however; and the "placebo response" argument, so far as I can make it out at all, seems more applicable to an observational study than to a randomized trial. In an observational study, perhaps, an unexpectedly good outcome in controls might suggest that the control group was not really an appropriate comparison group for the treated subjects; but such an argument cannot apply to a randomized trial. The "placebo response," whether it is truly a response to placebo, or regression, or anything else, must occur also in the active treatment group, unless the active treatment has a countervailing negative effect. If the active treatment had no effect at all, then the patients who did well on placebo would have done equally well on active treatment, and the bad luck consists of having randomly assigned so many of them to

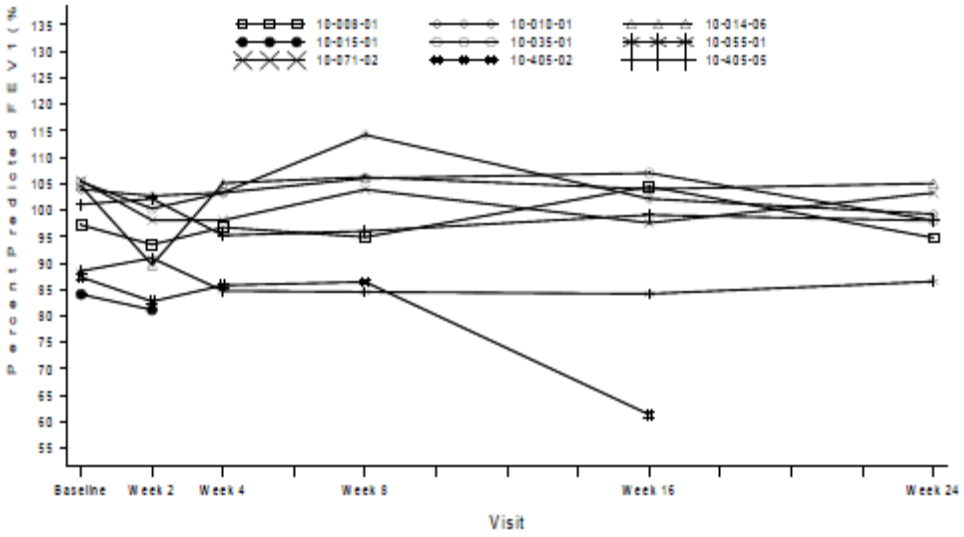
placebo. The probability of such bad luck is precisely what is represented by the p-value, and it is rather small. The "placebo response" in no way explains this.

Figure 11-19 Percent Predicted FEV_1 up to Week 24, Placebo Group; Full Analysis Set, Subjects 6 to 11 Years of Age (Inclusive)



Source: Figure 14.2.1.17ad.

Figure 11-20 Percent Predicted FEV_1 up to Week 24, Ivacaftor Group; Full Analysis Set, Subjects 6 to 11 Years of Age (Inclusive)



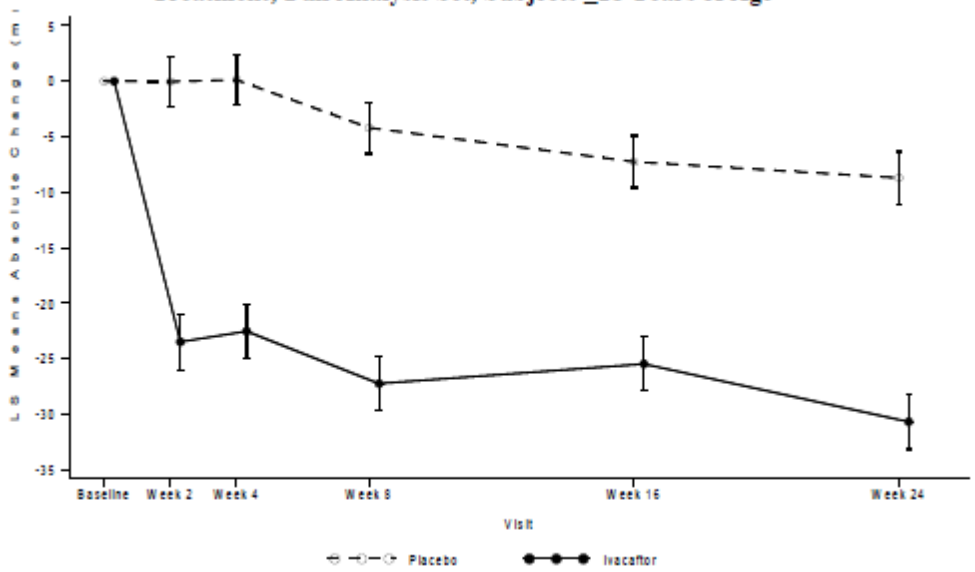
Source: Figure 14.2.1.17ad.

Notwithstanding the weakness of the applicant's argument, I agree that the most likely explanation for the discrepant results is a near-zero true effect in the pediatric patients, whose lung function was not much impaired to begin with, along with the play of chance. The possibility remains, however, that there may not be an effect at all, so that the result in adults, as in children, is a chance occurrence. I shall discuss this problem in detail below, after considering other evidence from study 110 and the extension study 112.

2.2 SECONDARY MEASURE

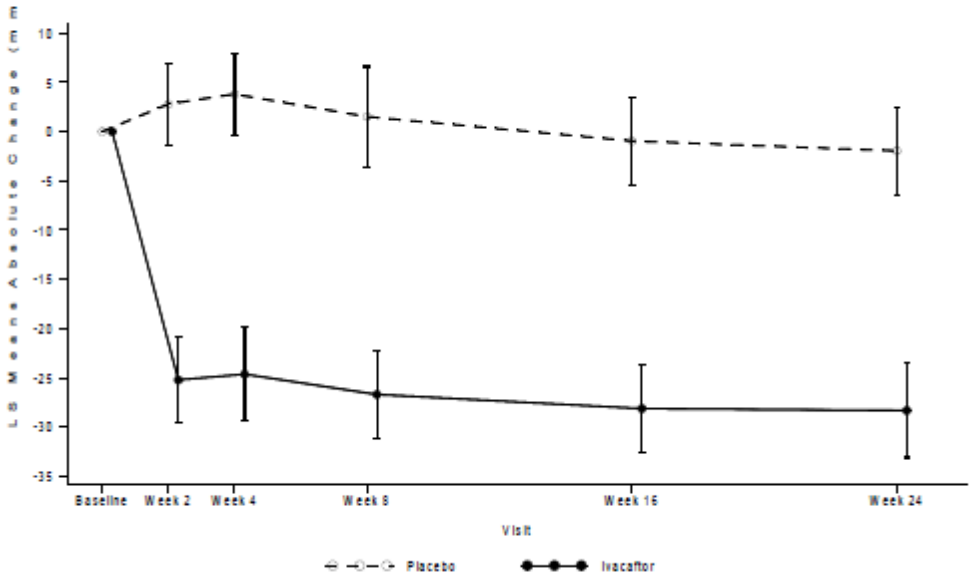
Sweat chloride is a diagnostic marker of cystic fibrosis, but it is not clear how reductions in sweat chloride relate to improvements in clinical outcomes. Sweat chloride was unquestionably reduced both in adults and in children (pp. 166, 185).

Figure 11-12 Mean Absolute Change From Baseline in Sweat Chloride (mmol/L) by Treatment; Full Analysis Set, Subjects ≥18 Years of Age



Source: Figure 14.2.2.5ad.

Figure 11-21 Mean Absolute Change From Baseline in Sweat Chloride (mmol/L) by Treatment; Full Analysis Set, Subjects 6 to 11 Years of Age (Inclusive)



Source: Figure 14.2.2.4ad.

2.3 OTHER PARTITIONS

Since the separate analysis of patients by age was after the fact (though regulations require the possibility of differential effects by age to be addressed), the question may arise as to whether other partitions might equally well account for the apparent difference in efficacy between adults and children. We considered especially partitions by baseline FEV_1 (<70% of predicted, between 70% and 90%, or above 90%) and by poly-T variant genotype (5T or 7T). These factors are both correlated with age: the children were less likely to have impaired function at baseline and more likely to have the 7T variant. Accordingly, rather than separate analyses of the primary outcome by baseline FEV_1 , age group, and poly-T variant, I computed a multiple regression including interactions of treatment with these three factors. There was a nominally significant interaction of treatment with age, and none of the other effects was remarkable. That is, there is a differential treatment effect by age even adjusting for possible differential effects by baseline function and poly-T variant.

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.9513215	0.990966	0.96	0.3413
AGEGR1[>=18]	-0.731575	1.517406	-0.48	0.6316
R117H_S[5T]	0.9305621	1.003818	0.93	0.3580
FEVGRP[<70%]	1.4353746	1.648539	0.87	0.3877
FEVGRP[>=70% to <=90%]	0.4865288	1.291455	0.38	0.7078
TRTA[Ivacaftor]	-0.782015	0.990966	-0.79	0.4334
AGEGR1[>=18]*TRTA[Ivacaftor]	4.108454	1.517406	2.71	0.0090*
FEVGRP[<70%]*TRTA[Ivacaftor]	-1.778651	1.648539	-1.08	0.2853
FEVGRP[>=70% to <=90%]*TRTA[Ivacaftor]	-1.073106	1.291455	-0.83	0.4096
R117H_S[5T]*TRTA[Ivacaftor]	0.6796797	1.003818	0.68	0.5012

Least Squares Means Table

Level	Least Sq Mean	Std Error
>=18,Ivacaftor	3.546186	1.7717320
>=18,Placebo	-3.106693	2.4100485
6 to 11,Ivacaftor	-3.207572	2.5812517
6 to 11,Placebo	6.573366	3.2658923

Tables generated by reviewer. Dependent variable is CHG (change from baseline) for AVISIT = "Average through Week 24" in data set adsp.xpt excluding subjects between 12 and 17 years old.

3 STUDY 112

Study 112 is an ongoing open-label extension to several different studies of ivacaftor in cystic fibrosis with various mutations. The submission and this review discuss a 12-week interim analysis of those patients previously enrolled in study 110. Most of the patients in study 110 enrolled in the extension. There was a 3- to 4-week washout, and then all patients received ivacaftor. The applicant analyzed the data in two groups: placebo/ivacaftor, meaning patients who had had placebo in study 110, and ivacaftor/ivacaftor, meaning patients who had had ivacaftor in study 110. Baseline here means a new baseline at the end of the washout. The table (summary of clinical efficacy addendum, p. 44) reports the change in FEV_1 (percent predicted) from the new baseline to week 2 and week 12 for patients over 18.

Table 11 Study 112: Absolute Change from Baseline to Week 2 and Week 12 in Percent Predicted FEV1, Full Analysis Set, Subjects ≥18 Years of Age

Study Population	Study Visit	N	Mean Change from Baseline (Percentage Points)	*P* value[a]
Overall	Week 2	49	3.8850	<0.0001
	Week 12	46	5.1489	<0.0001
Placebo/Ivacaftor	Week 2	26	4.7083	0.0022
	Week 12	26	5.4685	0.0016
Ivacaftor/Ivacaftor	Week 2	23	2.9544	0.0051
	Week 12	20	4.7334	0.0036

Source: Module 5.3.5.2/VX12-770-112/Table 2-4

Notes: Baseline was defined as the most recent measurement before intake of the first dose of study drug in Study 112. This measurement was taken at the Day 1 Visit for Study 112, which was also the Follow-up Visit of Study 110, and which occurred 3 to 4 weeks after the last dose of study drug in Study 110). Age is the baseline age in Study 110.

[a] *P* values are based on the one-sample t-test.

There was a substantial improvement from the new baseline with open-label treatment. Notably, the improvement was slightly more in the placebo/ivacaftor group than in the ivacaftor/ivacaftor group. If the result in adults of study 110 were a Type I error—that is, if ivacaftor had no effect and patients who were fated to do better had been randomly assigned to ivacaftor—one might have expected that same ivacaftor/ivacaftor group to do better again in the extension. The fact that the opposite happened, therefore, tends somewhat to reinforce the inference that the result in study 110 was not a Type I error but a real drug effect. This is in addition to the overall result in study 112, which is that the condition of all the patients improved substantially on average after beginning or resuming treatment with ivacaftor.

Baseline-controlled studies are of course subject to biases not found in concurrent-controlled studies. In combination with study 110, however, study 112 supports the hypothesis that there is a real, substantial, positive effect of ivacaftor on pulmonary function in adults with R117H.

4 STRENGTH OF EVIDENCE

The only concurrent-controlled study of ivacaftor in patients with the R117H mutation failed with respect to its primary measure of outcome. The Agency takes the prespecification of a primary outcome seriously. Only in this way can the probability of a false finding of efficacy for an ineffective drug be strictly controlled. If ivacaftor were completely ineffective, the primary analysis would nevertheless have succeeded with probability 0.025, and efficacy would have been erroneously inferred. Any post hoc analysis, also subject to error, can only add to this probability, and it is difficult to say by how much: it depends on the statistical relationship of the secondary measures to the primary measure; but especially it depends on how many equally plausible secondary analyses there might be, which is hard to make precise. Analysis of subgroups by age is required by regulation, along with race and sex, though there was no possibility of detecting a differential effect by race because all the patients, like almost the whole target population, were white. Genotype and baseline pulmonary function would likely also have been seen as plausible classifiers if a differential effect had been seen, compounding the problem of multiplicity. Thus, there is no way to find that the results of study 110 are statistically significant with respect to the usual but not absolute standard.

There are other kinds of inferential errors to be considered, however. The balance of Type I and Type II errors must always be taken into account, of course, but this is usually done by fixing the "regulator's risk" of Type I error and letting the sponsor control the "sponsor's risk" of Type II error through the sample size. Ivacaftor in cystic fibrosis, however, presents a more complex set of possible decisions and therefore more kinds of error than just falsely inferring efficacy for an ineffective drug or failing to infer efficacy for an effective one. The situation is this: ivacaftor has already been found to be an effective drug for some patients with cystic fibrosis. The question now is, What other patients does it work for? There will be many genotypes to consider, some of them so rare that it will not be possible to recruit enough patients to achieve statistical significance for a single genotype considered in isolation. That is not yet the case with R117H, but the problem is already apparent here. Suppose it is suspected that the drug may be effective in adults or in children but not necessarily in both. Within the usual regime of prespecified primary tests of significance, the sponsor has two choices. They can do separate studies in adults and children, controlling the probability of Type I error in each, and of Type II error as well if they can recruit enough patients. (Even so, there will be a multiplicity problem considering the two studies together: the probability of at least one Type I error out of two is nearly double the significance level, and similarly for Type II error.) Alternatively, they can conduct a single study and test the effect in adults and children combined. This approach offers control of the probability of both kinds of error assuming the effects in adults and children are truly same, but no control at all of any kind of error if they happen to be different. For example, if the drug is in fact effective in adults and not in children, the conclusion that it is effective in both is inevitably wrong in one group or the other, and likewise the conclusion that it is ineffective in both: a 100% probability of at least one error.

There was reason to think a priori that the effects in adults and children might be different. The children's pulmonary function was not yet so impaired as that of the adults, so that it

might be unsurprising not to see an effect in a 24-week study. Even though the sponsor chose to pool the results anyway for the primary analysis, so that it failed, I do not believe the negative results in children substantially diminish the strength of the evidence of a positive effect in adults.

Classical statistical methods generally involve either assuming effects are the same and pooling, or assuming they are different and treating them independently, sometimes with an unreliable preliminary test of whether they are different. Such methods are not well suited to answering the question of what groups ivacaftor works for. This will be a difficult question for very small groups, but it is not so difficult here. Study 110 provides reasonably strong evidence of an effect on pulmonary function in adults with mutation R117H, along with unquestionable evidence of an effect on sweat chloride both in adults and in children. Study 110 is corroborated to some extent by the open-label experience in study 112.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KALYDECO safely and effectively. See full prescribing information for KALYDECO.

KALYDECO® (ivacaftor) Tablets, for oral use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------
- Indications and Usage (1) 02/2014

----------INDICATIONS AND USAGE----------
KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. (1)

Limitations of Use
- Not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene. (1, 14)

----------DOSAGE AND ADMINISTRATION----------
- Adults and pediatric patients age 6 years and older: one 150 mg tablet taken orally every 12 hours with fat-containing food. (2.1, 12.3)
- Reduce dose in patients with moderate and severe hepatic impairment. (2.2, 8.6, 12.3)
- Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors. (2.3, 7.1, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 150 mg (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Elevated transaminases (ALT or AST): Transaminases (ALT and AST) should be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO dosing. (5.1, 6)
- Use with CYP3A inducers: Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's Wort) substantially decreases exposure of ivacaftor, which may diminish effectiveness. Therefore, co-administration is not recommended. (5.2, 7.2, 12.3)

----------ADVERSE REACTIONS----------
The most common adverse drug reactions to KALYDECO (occurring in ≥8% of patients with CF who have a *G551D* mutation in the *CFTR* gene) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness. (6.1)

----------DRUG INTERACTIONS ----------
CYP3A inhibitors: Reduce KALYDECO dose to 150 mg twice a week when co-administered with strong CYP3A inhibitors (e.g., ketoconazole). Reduce KALYDECO dose to 150 mg once daily when co-administered with moderate CYP3A inhibitors (e.g., fluconazole). Avoid food containing grapefruit or Seville oranges. (7.1, 12.3)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-752-5933 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Limitations of Use

KALYDECO is not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information in Adults and Children Ages 6 Years and Older

The recommended dose of KALYDECO for both adults and pediatric patients age 6 years and older is one 150 mg tablet taken orally every 12 hours (300 mg total daily dose) with fat-containing food. Examples of appropriate fat-containing foods include eggs, butter, peanut butter, cheese pizza, etc. [*see Clinical Pharmacology (12.3)* and *Patient Counseling Information (17.4)*].

2.2 Dosage Adjustment for Patients with Hepatic Impairment

The dose of KALYDECO should be reduced to 150 mg once daily for patients with moderate hepatic impairment (Child-Pugh Class B). KALYDECO should be used with caution in patients with severe hepatic impairment (Child-Pugh Class C) at a dose of 150 mg once daily or less frequently [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3),* and *Patient Counseling Information (17.3)*].

2.3 Dosage Adjustment for Patients Taking Drugs that are CYP3A Inhibitors

When KALYDECO is being co-administered with strong CYP3A inhibitors (e.g., ketoconazole), the dose should be reduced to 150 mg twice a week. The dose of KALYDECO should be reduced to 150 mg once daily when co-administered with moderate CYP3A inhibitors (e.g., fluconazole). Food containing grapefruit or Seville oranges should be avoided [*see Drug Interactions (7.1), Clinical Pharmacology (12.3),* and *Patient Counseling Information (17.2)*].

3 DOSAGE FORMS AND STRENGTHS

150 mg tablets.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Transaminase (ALT or AST) Elevations

Elevated transaminases have been reported in patients with CF receiving KALYDECO. It is recommended that ALT and AST be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO dosing [*see Adverse Reactions (6)*].

5.2 Concomitant Use with CYP3A Inducers

Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Therefore, co-administration of KALYDECO with strong CYP3A inducers (e.g., rifampin, St. John's Wort) is not recommended [*see Drug Interactions (7.2)* and *Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

The following adverse reaction is discussed in greater detail in other sections of the label:

- Transaminase Elevations [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The overall safety profile of KALYDECO is based on pooled data from three placebo-controlled clinical trials conducted in 353 patients with CF who had a *G551D* mutation in the *CFTR* gene (Trials 1 and 2) or were homozygous for the *F508del* mutation (Trial 3). In addition, an 8-week crossover design trial (Trial 4) involving 39 patients with a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* mutation in the *CFTR* gene was conducted. Patients treated with KALYDECO in these trials were between the ages of 6 and 57 years.

Of the 353 patients included in the pooled analyses of patients with CF who had either a *G551D* mutation or were homozygous for the *F508del* mutation in the *CFTR* gene, 50% of patients were female and 97% were Caucasian; 221 received KALYDECO and 132 received placebo from 16 to 48 weeks.

The proportion of patients who prematurely discontinued study drug due to adverse reactions was 2% for KALYDECO-treated patients and 5% for placebo-treated patients. Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in KALYDECO-treated patients included abdominal pain, increased hepatic enzymes, and hypoglycemia.

The most common adverse reactions in the 221 patients treated with KALYDECO were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%).

The incidence of adverse reactions below is based upon two double-blind, placebo-controlled, 48-week clinical trials (Trials 1 and 2) in a total of 213 patients with CF ages 6 to 53 who have a *G551D* mutation in the *CFTR* gene and who were treated with KALYDECO 150 mg orally or placebo twice daily. Table 1 shows adverse reactions occurring in ≥8% of KALYDECO-treated patients with CF who have a *G551D* mutation in the *CFTR* gene that also occurred at a higher rate than in the placebo-treated patients in the two double-blind, placebo-controlled trials.

Table 1: Incidence of Adverse Drug Reactions in ≥8% of KALYDECO-Treated Patients with a *G551D* Mutation in the *CFTR* Gene and Greater than Placebo in 2 Placebo-Controlled Phase 3 Clinical Trials of 48 Weeks Duration

	Incidence: Pooled 48-week Trials	
Adverse Reaction (Preferred Term)	**KALYDECO N=109 n (%)**	**Placebo N=104 n (%)**
Headache	26 (24)	17 (16)
Oropharyngeal pain	24 (22)	19 (18)
Upper respiratory tract infection	24 (22)	14 (14)
Nasal congestion	22 (20)	16 (15)
Abdominal pain	17 (16)	13 (13)
Nasopharyngitis	16 (15)	12 (12)
Diarrhea	14 (13)	10 (10)
Rash	14 (13)	7 (7)
Nausea	13 (12)	11 (11)
Dizziness	10 (9)	1 (1)

Adverse reactions in the 48-week clinical trials that occurred in the KALYDECO group at a frequency of 4 to 7% where rates exceeded that in the placebo group include:
Infections and infestations: rhinitis
Investigations: aspartate aminotransferase increased, bacteria in sputum, blood glucose increased, hepatic enzyme increased
Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, myalgia
Nervous system disorders: sinus headache
Respiratory, thoracic and mediastinal disorders: pharyngeal erythema, pleuritic pain, sinus congestion, wheezing
Skin and subcutaneous tissue disorders: acne

Laboratory Abnormalities
Transaminase Elevations During 48-week placebo-controlled clinical studies, the incidence of maximum transaminase (ALT or AST) >8, >5 or >3 x ULN was 2%, 3% and 6% in KALYDECO-treated patients and 2%, 2% and 8% in placebo-treated patients, respectively. Two patients (2%) on placebo and 1 patient (0.5 %) on KALYDECO permanently discontinued treatment for elevated transaminases, all >8 x ULN. Two patients treated with KALYDECO were reported to have serious adverse reactions of elevated liver transaminases compared to none on placebo [*see Warnings and Precautions (5.1)*].

The safety profile for the 39 patients with CF with a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* mutation enrolled in the 8-week crossover trial (Trial 4) was similar to that observed in the 48-week placebo-controlled trials (Trials 1 and 2).

7 DRUG INTERACTIONS

Potential for other drugs to affect ivacaftor

7.1 Inhibitors of CYP3A

Ivacaftor is a sensitive CYP3A substrate. Co-administration with ketoconazole, a strong CYP3A inhibitor, significantly increased ivacaftor exposure [measured as area under the curve (AUC)] by 8.5-fold. Based on simulations of these results, a reduction of the KALYDECO dose to 150 mg twice a week is recommended for co-administration with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin.

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased ivacaftor exposure by 3-fold. Therefore, a reduction of the KALYDECO dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

Co-administration of KALYDECO with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of ivacaftor. Therefore, food containing grapefruit or Seville oranges should be avoided during treatment with KALYDECO [*see Clinical Pharmacology (12.3)*].

7.2 Inducers of CYP3A

Co-administration with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor exposure (AUC) by approximately 9-fold. Therefore, co-administration with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's Wort is not recommended [*see Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

Potential for ivacaftor to affect other drugs

7.3 CYP3A and/or P-gp Substrates

Ivacaftor and its M1 metabolite have the potential to inhibit CYP3A and P-gp. Co-administration with midazolam, a sensitive CYP3A substrate, increased midazolam exposure 1.5-fold, consistent with weak inhibition of CYP3A by ivacaftor. Co-administration with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of KALYDECO may increase systemic exposure of drugs that are substrates of CYP3A and/or P-gp, which may increase or prolong their therapeutic effect and adverse events. Therefore, caution and appropriate monitoring are recommended when co-administering KALYDECO with CYP3A and/or P-gp substrates, such as digoxin, cyclosporine, and tacrolimus [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category B. There are no adequate and well-controlled studies of KALYDECO in pregnant women. Ivacaftor was not teratogenic in rats at approximately 6 times the maximum recommended human dose (MRHD) (based on summed AUCs for ivacaftor and its metabolites at a maternal dose of 200 mg/kg/day). Ivacaftor was not teratogenic in rabbits at approximately 12 times the MRHD (on an ivacaftor AUC basis at a maternal dose of 100 mg/kg/day, respectively). Placental transfer of ivacaftor was observed in pregnant rats and rabbits. Because animal reproduction studies are not always predictive of human response, KALYDECO should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Ivacaftor is excreted into the milk of lactating female rats. Excretion of ivacaftor into human milk is probable. There are no human studies that have investigated the effects of ivacaftor on breast-fed infants. Caution should be exercised when KALYDECO is administered to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of KALYDECO in patients 6 to 17 years of age with CF who have a *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R* mutation in the *CFTR* gene has been demonstrated [*see Adverse Reactions (6)* and *Clinical Studies (14)*].

The safety and efficacy of KALYDECO in patients with CF younger than age 6 years have not been established.

8.5 Geriatric Use

CF is largely a disease of children and young adults. Clinical trials of KALYDECO did not include sufficient numbers of patients 65 years of age and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A reduced dose of 150 mg once daily is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C) but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a dose of 150 mg once daily or less frequently in patients with severe hepatic impairment after weighing the risks and benefits of treatment [*see Pharmacokinetics (12.3)*].

8.7 Renal Impairment

KALYDECO has not been studied in patients with mild, moderate, or severe renal impairment or in patients with end-stage renal disease. No dose adjustment is necessary for patients with mild to moderate renal impairment; however, caution is recommended while using KALYDECO in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease.

8.8 Patients with CF who are Homozygous for the *F508del* Mutation in the *CFTR* Gene

Efficacy results from a double-blind, placebo-controlled trial in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene showed no statistically significant difference in forced expiratory volume exhaled in one second (FEV_1) over 16 weeks of KALYDECO treatment compared to placebo [*see Clinical Studies (14.3)*]. Therefore, KALYDECO should not be used in patients homozygous for the *F508del* mutation in the *CFTR* gene.

10 OVERDOSAGE

There have been no reports of overdose with KALYDECO.

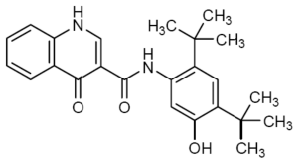
The highest single dose used in a clinical study was 800 mg in a solution formulation without any treatment-related adverse events.

The highest repeated dose was 450 mg (in a tablet formulation) every 12 hours for 4.5 days (9 doses) in a trial evaluating the effect of KALYDECO on ECGs in healthy subjects. Adverse events reported at a higher incidence compared to placebo included dizziness and diarrhea.

No specific antidote is available for overdose with KALYDECO. Treatment of overdose with KALYDECO consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

11 DESCRIPTION

The active ingredient in KALYDECO tablets is ivacaftor, which has the following chemical name: *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. Its molecular formula is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. Ivacaftor has the following structural formula:



Ivacaftor is a hi to off- h r that is practically i e (< ogram/mL).
KALYDECO lable as a ıe capsule-shaped, film- d t e or dmi : a on 150 mg of ivacaftor. Ea h t ble c i i c ve ingredients l l i ome ose t uc ina e a t monohydrate, magnesium stearate, mi c oc yst ll ce ose nc yl a a lm coat contains carnauba wax, FD&C Blue #2, P alcohol, talc, and titanium dioxide. The printing ink or s oxi r c ene glycol, and shellac.

12 CI MACOLOGY

12.1 i of Action

Ivacaftor a C pr a hlor de ha e e ırface of epithelial cells in multiple organs. Ivacaftor t e s i ransport by potentiating the channel-open probability or gating) of the CFTR protein.

caftor e FTR- nsepithelial current (I_T) n r e ls expressing the G551D-CFTR protein following addition of a cyclic ne t AMP) agonist with an EC_{50} o 100 ± ve , ivacaftor di t ıcrease I_T in the absence of cAMP agonist. Ivacaftor e d I_T l ells expressing G551D-CFTR ote n o l i t on of a cAMP agonist by 10-fold with an EC_{50} 236 ± 200 nM. I acaftor nc d the open probability of G551D-CFTR protein us m a pa c s fr odent s ing G551D-CFTR protein by 6- sus unt e t ll f e a i a . In addition to G551D-CFTR, ivacaftor increased the channel- probability of ıer mutant CFTR forms expressed in rodent cells, e il n e nc d CFTR-mediated I_T. These mutant CFTR forms included '8R-, S549N- 9R-, G551S-, G970R-, G1244E-, S1251N-, S1255P- and G1349D- FTR. c s r ly c e o vo pha onse or clinical benefit.

12.2 ynamics

Sweat C ide Evaluation

i e or onse to KALYDECO were va d in f li a t i ls n w ndomized, double-blind, placebo-c r le l c l tria s ith a *G551D* mut tion in the *CFTR* gene, one in patients 12 and older rial 1) and the ot er in patients 6-11 years of age (Trial 2), the r a me t difference (etween A CO and placebo) in nge a f se ne gh Week 24 was -48 mmol/L (95% CI -51, -45) and - o 95% CI -62, -47), respectively. These chang s pe e e ks. In a 16- andomized, double-blind, placebo- ont oll d, pa a le - with CF age 12- a de ho w e ygous for the *F508del* mutation in the *CFTR* gene (Trial 3), the treatment differ i ı li thr e e ent was - ol/L (95% CI -6, -0.2). In a two-part, randomized, double-bl , placebo- c l l ti nt wit wh l a 'S, G , *S1255P* ', or *S549R* tation in the gene (Trial 4), the treatment difference in n c n n sw t o ide from baseli through 8 weeks of treatment was - ol/L (95% CI -57, -41). In Trial 4, mean in swe t or de or he mutations w c Y) is indicated ranged from -51 to -78, whereas a f dual subjects with the *G970R* mutations was -1 to -11 mmol/L.

r l i between decrease in sweat c ve a m i unction (FEV_1).

ECG Ev tion

e int e l ed in a randomized, placeb o- and active-controlled c n 400 mg) four- T st a hy subj c . I t ility to detect small effects, the of the one- t l or r e djus d, baseline- or cted QTc based on Fridericia's correction method T hreshold for regulatory concern.

12.3 netics

pha okinetics of i ftor is similar between healthy adult volunteers and patients with CF.

t a ingle to healthy volunteers f d s t pe sm centrations (T_{max} occurred at approximately 4 hours, e (S and C_{max} 5260) r e i ly.

t 2- eady-state plasma c t c f or r a on r ti a ng f om

Absorption

The e of ivacaftor nc ased approximately 2- to 4-fold when given with f d containing fat herefore, KALYDECO should be administered with fat- i g food. E of fat-containing foods include eggs, but r butter, and he izza. The median (range) T_{max} is approximately 4.0 hou he

Distribution

Ivacaftor m e bound to plasma proteins, primarily to alpha 1- yc i lbumin. Ivacaftor does not bind to human red blood cells.

The mean e ume istribution (Vz/F) of ivacaftor after a single dose of 75 mg of LY DECO tate was similar for healthy subjects and patients with CF. 150 mg e r or l r n a a he mean (±SD) for appare volume o .

Metabolism

Ivacaftor is extensively metabolized in humans. In vitro and clinical studies indicate that ivacaftor is primarily metabolized by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth the potency of ivacaftor and is not considered pharmacologically active.

Elimination
Following oral administration, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent. The apparent terminal half-life was approximately 12 hours following a single dose. The mean apparent clearance (CL/F) of ivacaftor was similar for healthy subjects and patients with CF. The CL/F (SD) for the 150 mg dose was 17.3 (8.4) L/hr in healthy subjects.

Special populations
Hepatic impairment
Patients with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had similar ivacaftor C_{max}, but an approximately two-fold increase in ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics. Based on simulations of these results, a reduced KALYDECO dose of 150 mg once daily is recommended for patients with moderate hepatic impairment. The impact of mild hepatic impairment (Child-Pugh Class A) on pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than two-fold. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment. The impact of severe hepatic impairment (Child-Pugh Class C, score 10-15) on pharmacokinetics of ivacaftor has not been studied. The magnitude of increase in exposure in these patients is unknown but is expected to be substantially higher than that observed in patients with moderate hepatic impairment. When benefits are expected to outweigh the risks, KALYDECO should be used with caution in patients with severe hepatic impairment at a dose of 150 mg given once daily or less frequently.

Renal impairment
KALYDECO has not been studied in patients with mild, moderate or severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or in patients with end-stage renal disease. No dose adjustments are recommended for mild and moderate renal impairment patients because of minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine in a human PK study); however, caution is recommended when administering KALYDECO to patients with severe renal impairment or end-stage renal disease.

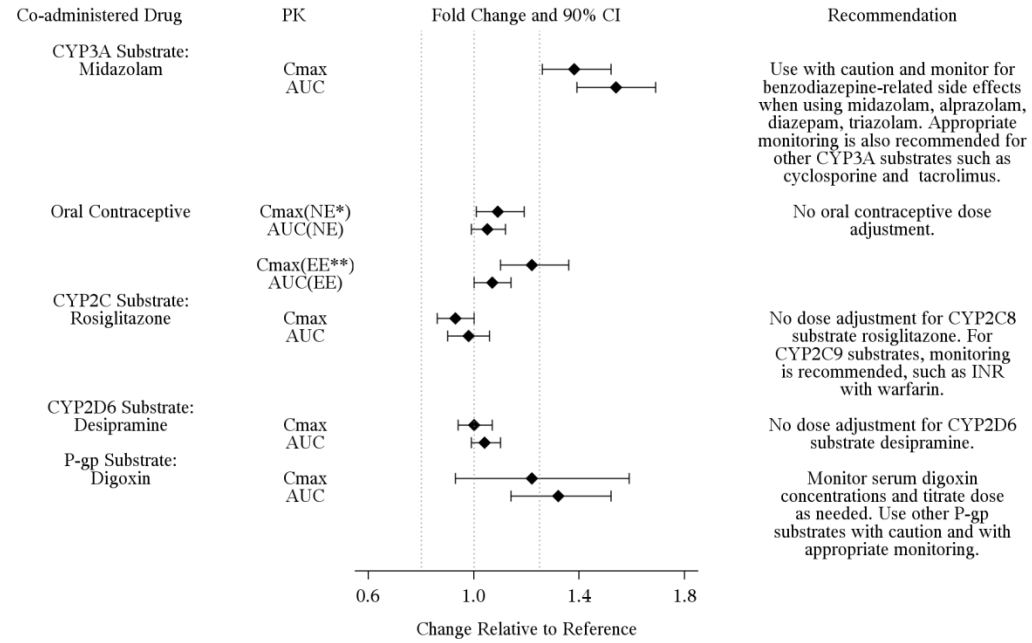
Gender
The effect of gender on KALYDECO pharmacokinetics was evaluated using population pharmacokinetics of data from clinical studies of KALYDECO. No dose adjustments are necessary based on gender.

Drug Interactions
Drug interaction studies were performed with KALYDECO and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies [*see Drug Interactions (7)*].

Dosing recommendations based on clinical studies or potential drug interactions with KALYDECO are presented below.

Potential for Ivacaftor to Affect Other Drugs
Based on in vitro results, ivacaftor and metabolite M1 have the potential to inhibit CYP3A and P-gp. Clinical studies showed that KALYDECO is a weak inhibitor of CYP3A and P-gp, but not an inhibitor of CYP2C8. In vitro studies suggest that ivacaftor and M1 may inhibit CYP2C9. In vitro, ivacaftor, M1, and M6 were not inducers of CYP isozymes. Dosing recommendations for co-administered drugs with KALYDECO are shown in Figure 1.

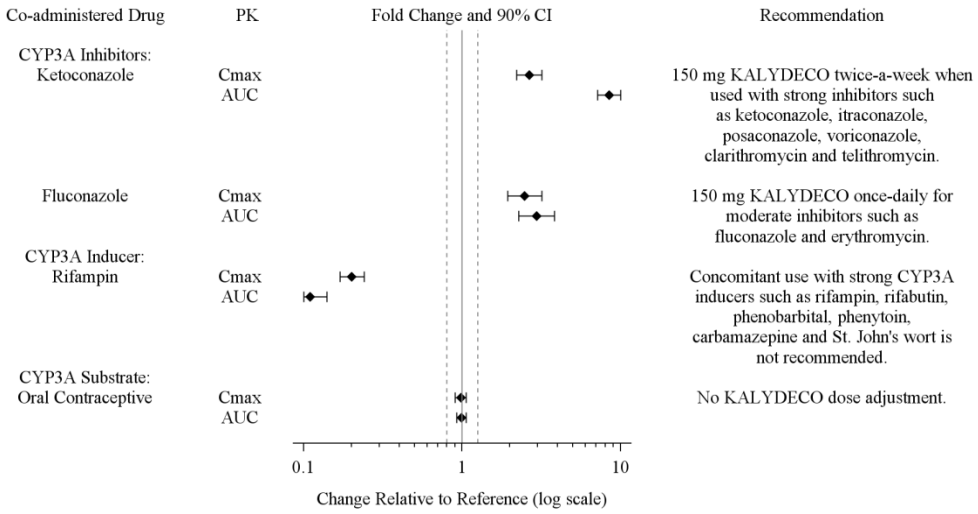
Figure 1: Impact of KALYDECO on Other Drugs



Note The data obtained with substrates but without co-administration of KALYDECO are used as reference.
*NE: Norethindrone; **EE: Ethinyl Estradiol
The vertical lines are at 0.8, 1.0 and 1.25, respectively.

Potential for Other Drugs to Affect Ivacaftor
In vitro studies showed that ivacaftor and metabolite M1 were substrates of CYP3A enzymes (i.e., CYP3A4 and CYP3A5). Exposure to ivacaftor is reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors [*see Dosage and Administration (2.3)* and *Drug Interactions (7)*]. KALYDECO dosing recommendations for co-administration with CYP3A inhibitors or inducers are shown in Figure 2.

Figure 2: Impact of Other Drugs on KALYDECO



Note The data obtained for KALYDECO without co-administration of inducers or inhibitors are used as reference. The vertical lines are at 0.8, 1.0 and 1.25, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year studies were conducted in mice and rats to assess carcinogenic potential of KALYDECO. No evidence of tumorigenicity was observed in mice or rats at ivacaftor oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to and 3 to 5 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 5 and 6 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 6 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (approximately 3 times the MRHD based on summed AUCs of ivacaftor and its metabolites).

13.2 Animal Toxicology and/or Pharmacology

Cataracts were seen in juvenile rats dosed with ivacaftor from postnatal day 7-35 at dose levels of 10 mg/kg/day and higher (approximately 0.12 times the MRHD based on summed AUCs of ivacaftor and its metabolites). This finding has not been observed in older animals.

14 CLINICAL STUDIES

14.1 Trials in Patients with CF who have a *G551D* Mutation in the *CFTR* Gene

Dose Ranging
Dose ranging for the clinical program consisted primarily of one double-blind, placebo-controlled, crossover trial in 39 adult (mean age 31 years) Caucasian patients with CF who had FEV_1 ≥40% predicted. Twenty patients with median predicted FEV_1 at baseline of 56% (range: 42% to 109%) received KALYDECO 25, 75, 150 mg or placebo every 12 hours for 14 days and 19 patients with median predicted FEV_1 at baseline of 69% (range: 40% to 122%) received KALYDECO 150, 250 mg or placebo every 12 hours for 28 days. The selection of the 150 mg every 12 hours dose was primarily based on nominal improvements in lung function (pre-dose FEV_1) and changes in pharmacodynamic parameters (sweat chloride and nasal potential difference). The twice-

daily dosing regimen was primarily based on an apparent terminal plasma half-life of approximately 12 hours. Selection of the 150 mg dose of KALYDECO for children 6 to 11 years of age was based on achievement of comparable pharmacokinetics as those observed for adult patients.

Efficacy

The efficacy of KALYDECO in patients with CF who have a *G551D* mutation in the *CFTR* gene was evaluated in two randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF (109 receiving KALYDECO 150 mg twice daily). All eligible patients from these trials were rolled over into an open-label extension study.

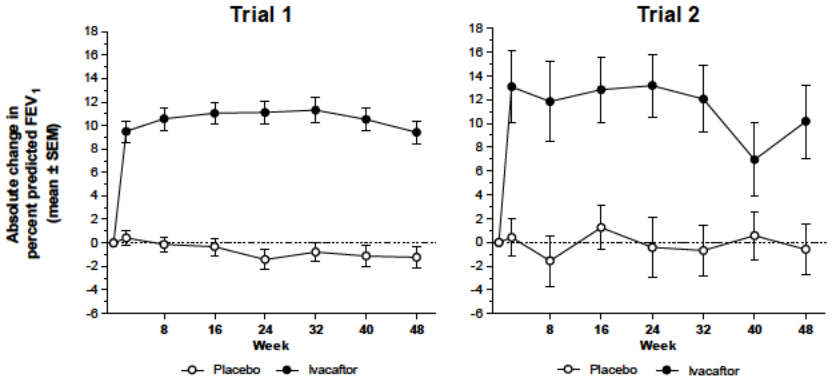
Trial 1 evaluated 161 patients with CF who were 12 years of age or older (mean age 26 years) with FEV_1 at screening between 40-90% predicted [mean FEV_1 64% predicted at baseline (range: 32% to 98%)]. Trial 2 evaluated 52 patients who were 6 to 11 years of age (mean age 9 years) with FEV_1 at screening between 40-105% predicted [mean FEV_1 84% predicted at baseline (range: 44% to 134%)]. Patients who had persistent *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal were excluded.

Patients in both trials were randomized 1:1 to receive either 150 mg of KALYDECO or placebo every 12 hours with food containing fat for 48 weeks in addition to their prescribed CF therapies (e.g., tobramycin, dornase alfa). The use of inhaled hypertonic saline was not permitted.

The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in percent predicted pre-dose FEV_1 through 24 weeks of treatment.

In both studies, treatment with KALYDECO resulted in a significant improvement in FEV_1. The treatment difference between KALYDECO and placebo for the mean absolute change in percent predicted FEV_1 from baseline through Week 24 was 10.6 percentage points ($P < 0.0001$) in Trial 1 and 12.5 percentage points ($P < 0.0001$) in Trial 2 (Figure 3). These changes persisted through 48 weeks. Improvements in percent predicted FEV_1 were observed regardless of age, disease severity, sex, and geographic region.

Figure 3: Mean Absolute Change from Baseline in Percent Predicted FEV_1 *



*Primary endpoint was assessed at the 24-week time point.

Other efficacy variables included absolute change in sweat chloride from baseline to Week 24 [*see Clinical Pharmacology (12.2)*], time to first pulmonary exacerbation through Week 48 (Trial 1 only), absolute change in weight from baseline to Week 48, and improvement in cystic fibrosis symptoms including relevant respiratory symptoms such as cough, sputum production, and difficulty breathing. For the purpose of the study, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. Patients treated with KALYDECO demonstrated statistically significant improvements in risk of pulmonary exacerbations, CF symptoms (in Trial 1 only), and gain in body weight (Table 2). Weight data, when expressed as body mass index normalized for age and sex in patients <20 years of age, was consistent with absolute change from baseline in weight.

Table 2: Effect of KALYDECO on Other Efficacy Endpoints in Trials 1 and 2

	Trial 1		Trial 2	
Endpoint	**Treatment difference[a] (95% CI)**	***P* value**	**Treatment difference[a] (95% CI)**	***P* value**
Mean absolute change from baseline in CF symptom score (points)				
Through Week 24	8.1 (4.7, 11.4)	<0.0001	6.1 (-1.4, 13.5)	0.1092
Through Week 48	8.6 (5.3, 11.9)	<0.0001	5.1 (-1.6, 11.8)	0.1354
Relative risk of pulmonary exacerbation				
Through Week 24	0.40[b]	0.0016	NA	NA
Through Week 48	0.46[b]	0.0012	NA	NA
Mean absolute change from baseline in body weight (kg)				
At Week 24	2.8 (1.8, 3.7)	<0.0001	1.9 (0.9, 2.9)	0.0004
At Week 48	2.7 (1.3, 4.1)	0.0001	2.8 (1.3, 4.2)	0.0002

CI: confidence interval; NA: not analyzed due to low incidence of events

[a] Treatment difference = effect of KALYDECO – effect of Placebo

[b] Hazard ratio for time to first pulmonary exacerbation

14.2 Trial in Patients with a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* Mutation in the *CFTR* Gene

The efficacy and safety of KALYDECO in patients with CF who have a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* mutation in the *CFTR* gene were evaluated in a two-part, randomized, double-blind, placebo-controlled, crossover design clinical trial in 39 patients with CF (Trial 4). Patients who completed Part 1 of this trial continued into the 16-week open-label Part 2 of the study. The mutations studied were *G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P,* and *G1349D.* See *Clinical Studies (14.1)* for efficacy in patients with a *G551D* mutation.

Patients were 6 years of age or older (mean age 23 years) with FEV_1 ≥40% at screening [mean FEV_1 at baseline 78% predicted (range: 43% to 119%)]. Patients with evidence of colonization with *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus* and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal at screening were excluded.

Patients were randomized 1:1 to receive either 150 mg of KALYDECO or placebo every 12 hours with food containing fat for 8 weeks in addition to their prescribed CF therapies during the first treatment period and crossed over to the other treatment for the second 8 weeks. The two 8-week treatment periods were separated by a 4- to 8-week washout period. The use of inhaled hypertonic saline was not permitted.

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV_1 through 8 weeks of treatment. Other efficacy variables included absolute change from baseline in sweat chloride through 8 weeks of treatment [*see Clinical Pharmacology (12.2)*], absolute change from baseline in body mass index (BMI) at 8 weeks of treatment (including body weight at 8 weeks), and improvement in cystic fibrosis symptoms (including relevant respiratory symptoms such as cough, sputum production, and difficulty breathing) through 8 weeks of treatment. For the overall population of the 9 mutations studied, treatment with KALYDECO compared to placebo resulted in significant improvement in percent predicted FEV_1 [10.7 through Week 8 ($P < 0.0001$)], BMI [0.66 kg/m^2 at Week 8 ($P < 0.0001$)], and cystic fibrosis respiratory symptom score [9.6 through Week 8 ($P = 0.0004$)]; however, there was a high degree of variability of efficacy responses among the 9 mutations (Table 3). Based on clinical and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the *G970R* mutation could not be established [*see Clinical Pharmacology (12.2)*].

Table 3: Effect of KALYDECO for Efficacy Variables in the Overall Populations and for Specific *CFTR* Mutations

Mutation (n)	Absolute change in percent predicted FEV_1			BMI (kg/m^2)	CF Respiratory Symptom Score (points)
	At Week 2	At Week 4	At Week 8	At Week 8	At Week 8
All patients (n=39) Results shown as mean (95% CI) change from baseline KALYDECO vs placebo-treated patients:					
	8.3 (4.5, 12.1)	10.0 (6.2, 13.8)	13.8 (9.9, 17.6)	0.66† (0.34, 0.99)	12.8 (6.7, 18.9)
Patients grouped under mutation types (n) Results shown as mean (minimum, maximum) for change from baseline for KALYDECO-treated patients*:					
G1244E (5)	11 (-5, 25)	6 (-5, 13)	8 (-1, 18)	0.63 (0.34, 1.32)	3.3 (-27.8, 22.2)
G1349D (2)	19 (5, 33)	18 (2, 35)	20 (3, 36)	1.15 (1.07, 1.22)	16.7 (-11.1, 44.4)
G178R (5)	7 (1, 17)	10 (-2, 21)	8 (-1, 18)	0.85 (0.33, 1.46)	20.0 (5.6, 50.0)
G551S (2)	0 (-5, 5)	0.3 (-5, 6)	3††	0.16††	16.7††
G970R (4)	7 (1, 13)	7 (1, 14)	3 (-1, 5)	0.48 (-0.38, 1.75)	1.4 (-16.7, 16.7)
S1251N (8)	2 (-23, 20)	8 (-13, 26)	9 (-20, 21)	0.73 (0.08, 1.83)	23.3 (5.6, 50.0)
S1255P (2)	11 (8, 14)	9 (5, 13)	3 (-1, 8)	1.62 (1.39, 1.84)	8.3 (5.6, 11.1)
S549N (6)	11 (5, 16)	8 (-9, 19)	11 (-2, 20)	0.79 (0.00, 1.91)	8.8 (-8.3, 27.8)
S549R (4)	3 (-4, 8)	4 (-4, 10)	5 (-3, 13)	0.53 (0.33, 0.80)	6.9 (0.0, 11.1)

* Statistical testing was not performed due to small numbers for individual mutations.
† Result for weight gain as a component of body mass index was consistent with BMI.
†† Reflects results from the one patient with the *G551S* mutation with data at the 8-week time point.

14.3 Trial in Patients Homozygous for the *F508del* Mutation in the *CFTR* Gene

Trial 3 was a 16-week randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene and who had FEV_1 ≥40% predicted. Patients were randomized 4:1 to receive KALYDECO 150 mg (n=112) every twelve hours or placebo (n=28) in addition to their prescribed CF therapies. The mean age of patients enrolled was 23 years and the mean baseline FEV_1 was 79% predicted (range 40% to 129%). As in Trials 1 and 2, patients who had persistent *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal were excluded. The use of inhaled hypertonic saline was not permitted.

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV_1. Treatment with KALYDECO resulted in no improvement in FEV_1 relative to placebo in patients with CF homozygous for the *F508del* mutation in the *CFTR* gene [mean absolute change from baseline through Week 16 in percent predicted FEV_1 was 1.5% and -0.2% for patients in the KALYDECO and placebo-treated groups, respectively ($P = 0.15$)]. There were no meaningful differences between patients treated with KALYDECO compared to placebo for secondary endpoints (change in CF symptoms, change in weight, or change in sweat chloride concentration).

16 HOW SUPPLIED/STORAGE AND HANDLING

KALYDECO® (ivacaftor) is supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor. Each tablet is printed with the characters "V 150" on one side and plain on the other, and is packaged as follows:

56-count carton (contains 4 individual blister cards of 14 tablets per card)	**NDC** 51167-200-01
60-count bottle	**NDC** 51167-200-02

Store at 20-25 C (68-77 F); excursions permitted to 15-30 C (59-86 F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

17.1 Transaminase (ALT or AST) Elevations and Monitoring

Inform patients that elevation in liver tests have occurred in patients treated with KALYDECO. Liver function tests will be performed prior to initiating KALYDECO, every 3 months during the first year of treatment and annually thereafter [*see Warnings and Precautions (5.1)*].

17.2 Drug Interactions with CYP3A Inducers and Inhibitors

Ask patients to tell you all the medications they are taking including any herbal supplements or vitamins. Co-administration of KALYDECO with strong CYP3A inducers (e.g., rifampin, St. John's Wort) is not recommended as they may reduce the therapeutic effectiveness of KALYDECO. Reduction of the dose of KALYDECO to 150 mg twice a week is recommended when co-administered with strong CYP3A inhibitors, such as ketoconazole. Dose reduction to 150 mg once daily is recommended when co-administered with moderate CYP3A inhibitors, such as fluconazole. Food containing grapefruit or Seville oranges should be avoided [*see Drug Interactions (7.1, 7.2)* and *Clinical Pharmacology (12.3)*].

17.3 Use in Patients with Hepatic Impairment

Inquire and/or assess whether patients have liver impairment. Reduce the dose of KALYDECO in patients with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) to 150 mg once daily. KALYDECO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C, score 10-15); however, exposure is expected to be substantially higher than that observed in patients with moderate hepatic impairment. When benefits are expected to outweigh the risks, KALYDECO should be used with caution in patients with severe hepatic impairment at a dose of 150 mg given once daily or less frequently. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A, score 5-6) [*see Clinical Pharmacology (12.3)*].

17.4 Take with Fat-Containing Food

Inform your patients that KALYDECO is best absorbed by the body when taken with food that contains fat. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, cheese pizza, etc.

VERTEX

Manufactured for
Vertex Pharmaceuticals Incorporated
Boston, MA 02210

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Revised June 2014

Patient Information is perforated for dispensing to the patient.

PATIENT INFORMATION

KALYDECO (kuh-LYE-deh-koh) (ivacaftor) Film-Coated Tablets

Read this Patient Information before you start taking KALYDECO and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is KALYDECO?

KALYDECO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following mutations in their CF gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*.

KALYDECO is not for use in people with CF due to other mutations in the CF gene. KALYDECO is not effective in CF patients with two copies of the *F508del* mutation (*F508del/F508del*) in the CF gene.

It is not known if KALYDECO is safe and effective in children under 6 years of age.

Who should not take KALYDECO?

Do not take KALYDECO if you take certain medicines or herbal supplements such as:

- the antibiotics rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medications such as phenobarbital, carbamazepine (Tegretol®, Carbatrol®, Equetro®) or phenytoin (Dilantin®, Phenytek®)
- St. John's Wort

Talk to your doctor before taking KALYDECO if you take any of the medicines or supplements listed above.

What should I tell my doctor before taking KALYDECO?

Before you take KALYDECO, tell your doctor if you:

- have liver or kidney problems
- drink grapefruit juice, or eat grapefruit or Seville oranges
- are pregnant or plan to become pregnant. It is not known if KALYDECO will harm your unborn baby. You and your doctor should decide if you will take KALYDECO while you are pregnant.
- are breastfeeding or planning to breastfeed. It is not known if KALYDECO passes into your breast milk. You and your doctor should decide if you will take KALYDECO while you are breastfeeding.

KALYDECO may affect the way other medicines work, and other medicines may affect how KALYDECO works.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements, as the dose of KALYDECO may need to be adjusted when taken with certain medications.

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Especially tell your doctor if you take:
- antifungal medications such as ketoconazole (e.g., Nizoral®), itraconazole (e.g., Sporanox®), posaconazole (e.g., Noxafil®), voriconazole (e.g., Vfend®), or fluconazole (e.g., Diflucan®)
- antibiotics such as telithromycin (e.g., Ketek®), clarithromycin (e.g., Biaxin®), or erythromycin (e.g., Ery-Tab®)

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take KALYDECO?

- Take KALYDECO exactly as your doctor tells you to take it.
- Always take KALYDECO with food that contains fat. Examples of fat-containing foods include eggs, butter, peanut butter, cheese pizza, etc.
- Your doses of KALYDECO should be taken 12 hours apart.
- Each KALYDECO box contains 4 individual blister cards.
- Each blister card contains 14 pills—7 morning doses and 7 evening doses.
- In the morning, unpeel the paper backing from a blister card to remove 1 KALYDECO pill and take it with food that contains fat.
- In the evening, 12 hours later, open another blister card to remove 1 KALYDECO pill and take it with food that contains fat.
- You may cut along the dotted line to separate your doses from the blister card.

What should I avoid while taking KALYDECO?
- KALYDECO can cause dizziness in some people who take it. Do not drive a car, use machinery or do anything that needs you to be alert until you know how KALYDECO affects you.
- You should avoid food containing grapefruit or Seville oranges while you are taking KALYDECO.

What are the possible side effects of KALYDECO?

KALYDECO can cause serious side effects.

High liver enzymes in the blood have been reported in patients receiving KALYDECO.
Your doctor will do blood tests to check your liver:
- before you start KALYDECO
- every 3 months during your first year of taking KALYDECO
- every year while you are taking KALYDECO

Call your doctor right away if you have any of the following symptoms of liver problems:
- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite

- nausea or vomiting
- dark, amber-colored urine

The most common side effects of KALYDECO include:

- headache
- upper respiratory tract infection (common cold), including:
  - sore throat
  - nasal or sinus congestion
  - runny nose
- stomach (abdominal) pain
- diarrhea
- rash
- nausea
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of KALYDECO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KALYDECO?

- Store KALYDECO at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Do not use KALYDECO after the expiration date on the package.

Keep KALYDECO and all medicines out of the reach of children.

General information about KALYDECO

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KALYDECO for a condition for which it was not prescribed. Do not give KALYDECO to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about KALYDECO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about KALYDECO that is written for health professionals.

For more information, go to www.kalydeco.com or call 1-877-752-5933.

What are the ingredients in KALYDECO?

Active ingredient: ivacaftor
Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

The tablet film coat contains: carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide.

The printing ink contains: ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

Approved June 2014

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